

THE ESSENTIAL GUIDE TO THE EVIDENCE
BEHIND CLINICAL PRACTICE

OXFORD HANDBOOK OF KEY CLINICAL EVIDENCE

EDITED BY Kunal Kulkarni | James Harrison
Mohamed Baguneid | Bernard Prendergast

Summarises and explains key papers which
influence current medical and surgical practice

Carefully selected and reviewed by specialists
for their relevance

Includes a brand new chapter on paediatrics,
as well as new trials reflecting recent developments



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**Oxford Handbook of
Key Clinical
Evidence**

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Oxford Handbook of Key Clinical Evidence

Second Edition

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Foreword to the second edition

Twenty years ago, David Sackett defined Evidence-Based Medicine as the integration of evidence, expertise and patient values to better underpin decision making.¹ Clinical evidence therefore underpins effective treatment decisions, and to improve patient care, expert clinicians have learnt to share evidence and decision making. Evidence is therefore at the core of effective patient care, decisions and actions. However, the considerable growth in the quantity of evidence published—seventy-five trials and eleven systematic reviews a day²—has made it increasingly difficult, if not impossible, for clinicians to keep up to date with the evidence that impacts directly on patient care.

The *Oxford Handbook of Key Clinical Evidence* can therefore act as an aid to the busy clinician: summaries for each key clinical area reduce the time to find the important influential trial evidence. By using impact on clinical practice as key criteria for selecting evidence, along with reviewing only those key issues that matter for a given topic area, the number needed to read to find important and impactful articles is significantly reduced. Furthermore, by selecting randomized controlled trials, wherever possible, for the summaries of treatment effects further focuses the reader to higher quality evidence that matters.

Every clinician should know the important evidence in a given topic area. This can be rapidly accessed from the handy summaries, the critical discussion and the highlighted problems encountered for each treatment effect. From the early chapters, you will be made aware of some of the important critical appraisal points that allow more in-depth critical analysis of evidence. There are two key issues to keep in mind when deciding to applying evidence to patients: (1) does this evidence apply to my patient (external validity); and (2) will it make a difference (clinical significance) to my patient? This book allows both of these questions to be readily answered. If the answer is yes to these two questions then the next question should consider the extent to which any biases in the methods or reporting (internal validity) might affect the stated treatment effect.

How would I read such a book? Periodical review of a topic area, analysis of an individual trial, on occasion review of the full publication, and through the use of critical appraisal skills take account of the important methodological considerations. And finally, work out a system for asking questions about patient care, recording them and accessing the best available evidence (e.g. systematic reviews and randomized controlled trials) as it emerges.

Thirty-five years ago Archie Cochrane pointed out that medicine had not produced a 'critical summary, by speciality or sub-speciality, adapted periodically, of all relevant randomised controlled trials.'³ This book is a great starting point for critically summarizing all of the relevant randomized trial evidence in a subspecialty and the journey for better-equipped evidence-based practice.

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1 Sackett DL, Rosenberg WM, Gray JA et al. (1996). Evidence based medicine: what it is and what it isn't. *BMJ* 312(7023):71–2.


2 Bastian H, Glasziou P, Chalmers I (2010). Seventy-Five Trials and Eleven Systematic Reviews a Day: How Will We Ever Keep Up? *PLoS Med* 7(9): e1000326. doi:10.1371/journal.pmed.1000326

3 Cochrane AL (1979). 1931–1971: a critical review, with particular reference to the medical profession. *Medicines for the Year 2000*. London: Office of Health Economics. pp. 1–11.

Preface to the second edition

If you are reading this book, then you probably have at least a vague interest in EBM (evidence-based medicine). After all, it is an inescapable buzzword in modern medicine and provokes an extreme range of reactions—from repulsion, to a belief in it as the panacea of sound clinical practice. Regardless of your preconceptions, our aim for this book has always been simple: to demonstrate that EBM is an accessible and valuable tool when applied in the appropriate clinical context. For this refreshed second edition, we have aimed to maintain this straightforward approach to the interpretation of EBM.

The greatest difficulty with EBM is that different readers will interpret a paper differently; for example, an academic's or a statistician's view may be markedly distinct from that of a clinician. Both may be correct in their analysis, but their differing backgrounds, experiences, and ultimate goals yield differences of opinion in their conclusions. In many cases, it can simply be a lack of training that leads to avoidance of critique in certain aspects of a paper. For example, medical students receive little exposure to applied statistics during their training, making critique of the results section a frightening task. Not knowing how and where to look can make EBM seem an untamable beast best left for someone else to deal with. However, without rigorous scrutiny, EBM is meaningless. External factors, such as cost and bureaucracy, are inherent to all health-care systems but should not restrict the contribution of high-quality evidence to clinical advances. Our hope is that this book will join the many resources that have sprung up in recent years to ensure that EBM remains free from undue influences and becomes a subject that is part-and-parcel of everyday clinical practice for health-care workers of all levels and backgrounds.

We have attempted to strike a balance between complexity and accessibility in ensuring that primary scientific and statistical facts are interpreted within a practical clinical context. The introductory chapters provide the background and framework for this process, while the template-based interpretations of our expert clinicians demonstrate the process of critical analysis of papers that have made key changes to their clinical practice. This book will attract comments and, no doubt, criticism. It is not all-encompassing, and there are unavoidable gaps. One such omission from the first edition (that we have now addressed) was the exclusion of Paediatrics—a specialty that has embraced the challenges of EBM in a complex patient population. EBM is an inexact science, with opinion and consensus forming a valuable component of its safe application to clinical practice. We welcome your feedback (please submit this via the book's page on the OUP website— <http://www.oup.com/uk/medicine/handbooks>). We appreciate the opinions of our readers and will endeavour to incorporate suggested changes into future editions.

Acknowledgements

Once again, we are indebted to all those at OUP that have helped put this book together. In addition to the many behind-the-scenes team members (whom we apologise for not naming individually here) we would like to thank several key people.

From the first edition, we thank our original commissioning editor Liz Reeve, who together with Beth Womack, Bethan Lee, Kate Wilson, Joyce Cheung and Andrew Sandland, helped deliver the first incarnation of this book into the world.

For this second edition, we have acquired more invaluable team members, including Michael Hawkes (Assistant Commissioning Editor), Katie Bishop (Editorial Assistant) and Fiona Chippendale (Production Editor), to whom we are incredibly grateful for maintaining momentum. Liz and Joyce, keen to endure the suffering once more, also joined us again, and their bravery has not gone unnoticed.

Finally, but most importantly, we would like to take this opportunity to once again recognize and thank our many expert contributors. This book is the product of their expert knowledge and dedication. Through their endeavours, hopefully EBM has been made a more accessible subject for all.

KK, JH, MB, BP

Contents

Contributors to the second edition [xi](#)

Contributors to the first edition [xv](#)

Symbols and abbreviations [xviii](#)

How to use this book [xxxvii](#)

Part 1 Introduction

| | | |
|---|--|----|
| 1 | The history of evidence-based medicine | 3 |
| 2 | An introduction to evidence-based medicine | 33 |

Part 2 Medical specialties

| | | |
|----|---|-----|
| 3 | Cardiology | 55 |
| 4 | Dermatology | 101 |
| 5 | Diabetes | 127 |
| 6 | Emergency medicine | 149 |
| 7 | Endocrinology | 179 |
| 8 | Gastroenterology | 205 |
| 9 | Genitourinary medicine | 241 |
| 10 | Geriatric medicine | 263 |
| 11 | Haematology | 287 |
| 12 | HIV medicine | 313 |
| 13 | Infectious diseases and tropical medicine | 329 |
| 14 | Neurology | 347 |
| 15 | Psychiatry | 387 |
| 16 | Renal medicine | 419 |
| 17 | Respiratory medicine | 447 |
| 18 | Rheumatology | 485 |

Part 3 Paediatrics

| | | |
|----|-------------|-----|
| 19 | Paediatrics | 511 |
|----|-------------|-----|

Part 4 Surgical specialties

| | | |
|----|--|-----|
| 20 | Anaesthetics | 537 |
| 21 | Breast surgery | 559 |
| 22 | Cardiac surgery | 591 |
| 23 | Gastrointestinal and hepatobiliary surgery | 611 |
| 24 | Intensive care | 649 |
| 25 | Neurosurgery | 673 |
| 26 | Obstetrics and gynaecology | 707 |
| 27 | Ophthalmology | 737 |
| 28 | Otorhinolaryngology | 765 |
| 29 | Plastic and reconstructive surgery | 795 |
| 30 | Transplantation | 815 |
| 31 | Trauma and orthopaedics | 839 |
| 32 | Urology | 869 |
| 33 | Vascular surgery | 897 |

| | |
|-------|-----|
| Index | 925 |
|-------|-----|

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Symbols and abbreviations

| | |
|-------|---|
| 📖 | book symbol |
| ~ | approximately |
| ° | degree |
| → | leads to |
| -ve | negative |
| +ve | positive |
| % | percentage |
| ± | plus or minus |
| ♀ | female |
| ♂ | male |
| 1° | primary |
| 2° | secondary |
| ∞ | infinity |
| = | equal to |
| > | greater than |
| < | less than |
| ≥ | equal to or greater than |
| ≤ | equal to or less than |
| α | alpha |
| β | beta |
| χ | chi |
| γ | gamma |
| £ | pound sterling |
| \$ | dollar |
| ® | registered |
| ™ | trademark symbol |
| AAA | abdominal aortic aneurysm |
| ABG | arterial blood gas |
| ABPI | ankle–brachial pressure index |
| ACE | angiotensin-converting enzyme |
| ACE-I | angiotensin-converting enzyme inhibitor |
| ACL | anterior cruciate ligament |

| | |
|----------|--|
| ACR | American College of Rheumatology |
| ACS | acute coronary syndrome |
| ACV | aciclovir |
| AD | Alzheimer's disease |
| ADCS-ADL | Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory |
| ADHD | attention-deficit/hyperactivity disorder |
| ADL | activity of daily living |
| ADP | adenosine diphosphate |
| ADPKD | autosomal dominant polycystic kidney disease |
| AED | antiepileptic drug |
| AF | atrial fibrillation |
| AH | alcoholic hepatitis |
| AHI | Apnoea/Hypopnoea Index |
| AI | aromatase inhibitor |
| AIDS | acquired immune deficiency syndrome |
| AIS | acute ischaemic stroke |
| ALI | acute lung injury |
| ALL | acute lymphoblastic leukaemia |
| ALP | alkaline phosphatase |
| ALS | amyotrophic lateral sclerosis |
| ALT | alanine transaminase |
| a.m. | <i>ante meridiem</i> (before noon) |
| AMD | age-related macular degeneration |
| AMI | acute myocardial infarction |
| AML | acute myeloid leukaemia |
| AMP | adenosine monophosphate |
| AMTS | abbreviated mental test score |
| ANCA | anti-neutrophil cytoplasmic antigen |
| AOM | acute otitis media |
| APACHE | acute physiology and chronic health evaluation |
| APAP | autotitrating positive airway pressure |
| APML | acute promyelocytic leukaemia |
| APT | adaptive pacing therapy |
| APTT | activated partial thromboplastin time |

| | |
|----------|--|
| ARDS | acute respiratory distress syndrome |
| ARF | acute renal failure |
| ARR | absolute risk reduction |
| ART | antiretroviral therapy |
| ASA | American Society of Anesthesiologists |
| ASA-ERDP | aspirin plus extended-release dipyridamole |
| AST | aspartate transaminase |
| AT | anaerobic threshold |
| ATG | antithymocyte globulin |
| ATO | arsenic trioxide |
| ATRA | all-trans-retinoic acid |
| AUA | American Urological Association |
| AUC | area under curve |
| AUR | acute urinary retention |
| AVR | aortic valve replacement |
| AVVSS | Aberdeen Varicose Vein Symptom Severity Score |
| AZA | azathioprine |
| BAI | Beck Anxiety Inventory |
| BALP | bone-specific alkaline phosphatase |
| BASDAI | Bath ankylosing spondylitis disease activity index |
| BASFI | Bath ankylosing spondylitis functional index |
| BASMI | Bath ankylosing spondylitis metrology index |
| BCC | basal cell carcinoma |
| BCG | bacille Calmette–Guérin |
| BCS | breast-conserving surgery |
| bd | bis in die (twice daily) |
| BDI | Beck Depression Inventory |
| BDP | beclomethasone dipropionate |
| BFZ | bendroflumethiazide |
| β-HCG | beta-human chorionic gonadotrophin |
| BHIVA | British HIV Association |
| BILAG | British Isles Lupus Assessment Group |
| BIS | bispectral index |
| BMI | body mass index |
| BMS | bare-metal stent |

| | |
|-----------|--|
| BMT | bone marrow transplant |
| BP | blood pressure; bullous pemphigoid |
| BPG | benzathine penicillin G |
| BPH | benign prostatic hyperplasia |
| bpm | beat per minute |
| BPPV | benign paroxysmal positional vertigo |
| BPRS | Brief Psychiatric Rating Scale |
| BRVO | branch retinal vein occlusion |
| BSA | body surface area |
| BSCVA | best spectacle-corrected visual acuity |
| BSER | brainstem-evoked response |
| BT | behaviour therapy |
| CABG | coronary artery bypass graft |
| CAD | coronary artery disease |
| CAS | carotid artery stenting |
| CBIC-Plus | Clinician's Interview-Based Impression of Change plus Care-giver Input |
| CBT | cognitive behavioural therapy |
| CBZ | carbamazepine |
| CCF | congestive cardiac failure |
| CD | cluster of differentiation; Crohn's disease |
| CDR | clinical decision rule |
| CEA | carotid endarterectomy; carcinoembryonic antigen |
| CEAP | clinical aetiologic anatomic pathophysiology |
| CES-D | Centre for Epidemiological Studies Depression Scale |
| CF | cystic fibrosis |
| CFS | chronic fatigue syndrome |
| CGI | Clinical Global Impression |
| CGIC | Clinical Global Impression of Change |
| CHD | coronary heart disease |
| CHEI | cholinesterase inhibitor |
| CHF | chronic heart failure |
| CHOP | cyclophosphamide, doxorubicin, vincristine, and prednisolone |
| CI | confidence interval |
| CIN | cervical intraepithelial neoplasia |

| | |
|-----------------|--|
| CKD | chronic kidney disease |
| cm | centimetre |
| CMAI | Cohen–Mansfield Agitation Inventory |
| CML | chronic myeloid leukaemia |
| CMML | chronic myelomonocytic leukaemia |
| CMV | cytomegalovirus |
| CNI | calcineurin inhibitor |
| CNS | central nervous system |
| CO ₂ | carbon dioxide |
| COPD | chronic obstructive pulmonary disease |
| COX | cyclo-oxygenase |
| CPAP | continuous positive airways pressure |
| CPX | cardiopulmonary exercise |
| CR1 | first complete remission |
| CRBSI | catheter-related bloodstream infection |
| CRC | colorectal cancer |
| CRDQ | chronic respiratory disease questionnaire |
| CrI | credible interval |
| CRP | C-reactive protein |
| CRS | chronic rhinosinusitis |
| CRT | cardiac resynchronization therapy; central retinal thickness |
| CRVO | central retinal vein occlusion |
| CsA | ciclosporin |
| CSF | cerebrospinal fluid |
| CSII | continuous subcutaneous insulin infusion |
| CSM | Committee on Safety of Medicines |
| CSMO | clinically significant macular oedema |
| C-spine | cervical spine |
| CSS | Clinical Severity Score |
| CT | computed tomography; cognitive therapy |
| CTA | computed tomography angiography |
| CV | cardiovascular |
| CVA | cerebrovascular accident |
| CVC | central venous catheter |

| | |
|--------|---|
| CVP | central venous pressure |
| d | day(s) |
| D | diopetre |
| 2D | two-dimensional |
| 3D | three-dimensional |
| DAA | directly acting antiviral |
| DAS | Disease Activity Score |
| dB | decibel |
| DBD | donation after brain death |
| DBP | diastolic blood pressure |
| DCD | donation after circulatory death |
| DCIS | ductal carcinoma <i>in situ</i> |
| DDH | developmental dysplasia of the hip |
| DES | drug-eluting stent |
| DEX | dexamethasone |
| DEXA | dual-energy X-ray absorptiometry |
| DF | discriminant factor |
| DFS | disease-free survival |
| D-HAQ | Dutch version of the Health Assessment Questionnaire |
| DHP | Dix–Hallpike |
| dL | decilitre |
| DLBCL | diffuse large B-cell lymphoma |
| DLQI | dermatology life quality index |
| DM | diabetes mellitus |
| DMARD | disease-modifying anti-rheumatic drug |
| DNA | deoxyribonucleic acid |
| DRE | digital rectal examination |
| DSA | digital subtraction angiography |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DVT | deep vein thrombosis |
| EAU | European Association of Urology |
| EASI | eczema area and severity index |
| EAT | Eating Attitudes Test |
| EBCTCG | Early Breast Cancer Trialists' Collaborative Group |

| | |
|-------|--|
| EBM | evidence-based medicine |
| EBRT | external beam radiotherapy |
| ECG | electrocardiogram |
| echo | echocardiography |
| EC-IC | extracranial–intracranial |
| ECMO | extracorporeal membrane oxygenation |
| ECOG | Eastern Cooperative Oncology Group |
| ECT | electroconvulsive therapy |
| ED | emergency department; erectile dysfunction |
| EDE | Eating Disorders Examination |
| EDSS | Expanded Disability Status Scale |
| EEG | electroencephalogram |
| EF | ejection fraction |
| EFS | event-free survival |
| EGDT | early goal-directed therapy |
| eGFR | estimated glomerular filtration rate |
| EGFR | epidermal growth factor receptor |
| ELISA | enzyme-linked immunosorbent assay |
| EM | Epley's manoeuvre |
| ENT | ear, nose, and throat |
| EORTC | European Organisation for Research and Treatment of Cancer |
| ER | oestrogen receptor |
| ERCP | endoscopic retrograde cholangio-pancreatography |
| ERDP | extended-release dipyridamole |
| ERP | enhanced recovery pathway |
| ESA | erythropoiesis-stimulating agent |
| ESR | erythrocyte sedimentation rate |
| ESRD | end-stage renal disease |
| ESRF | end-stage renal failure |
| ESWL | extracorporeal shock wave lithotripsy |
| ETDRS | Early Treatment of Diabetic Retinopathy Study |
| EVAR | endovascular aneurysm repair |
| EVLA | endovenous laser ablation |
| EVLP | ex vivo lung perfusion |

| | |
|------------------|--|
| FAOS | Foot and Ankle Outcome Score |
| FAST | Functional Assessment Staging scale |
| FCV | famciclovir |
| FDA | (US) Food and Drug Administration |
| FDP | flexor digitorum profundus |
| FDS | flexor digitorum superficialis |
| FEV | forced expiratory volume |
| FEV ₁ | forced expiratory volume in 1 second |
| FGF23 | fibroblast growth factor 23 |
| FICB | fascia iliaca compartment blockade |
| FiO ₂ | fraction of inspired oxygen |
| FISH | fluorescence <i>in situ</i> hybridization |
| FOB | faecal occult blood |
| FOBT | faecal occult blood testing |
| FS | flexible sigmoidoscopy; foam sclerotherapy |
| FT | family therapy |
| F/U | follow-up |
| 5-FU | 5-fluorouracil |
| FVC | forced vital capacity |
| g | gram |
| GA | general anaesthesia |
| GBP | gabapentin |
| GBS | Guillain–Barré syndrome |
| GC | gonococcus |
| GCS | Glasgow coma score |
| G-CSF | granulocyte colony-stimulating factor |
| GDS | Global Deterioration Scale |
| GET | graded exercise therapy |
| GFR | glomerular filtration rate |
| GI | gastrointestinal |
| GLP-1 | glucagon-like peptide-1 |
| GMP | guanosine monophosphate |
| GORD | gastro-oesophageal reflux disease |
| GOS | Glasgow Outcome Scale |
| GP | general practice/practitioner |

| | |
|-------------------|---------------------------------------|
| GSS | genotypic sensitivity score |
| GSV | great saphenous vein |
| GTR | gross total resection |
| GUM | genitourinary medicine |
| GWAS | genome-wide association study |
| Gy | gray |
| h | hour |
| HA | hydroxyapatite |
| HAART | highly active antiretroviral therapy |
| HAD | hospital anxiety and depression |
| Ham-A | Hamilton Anxiety Scale |
| HAMD | Hamilton Rating Scale for Depression |
| HAQ | Health Assessment Questionnaire |
| Hb | haemoglobin |
| HbA _{1c} | glycated haemoglobin |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HDL | high-density lipoprotein |
| HDU | high dependency unit |
| HF | heart failure |
| HFO | high-frequency oscillation |
| HIV | human immunodeficiency virus |
| HLA | human leucocyte antigen |
| HMGCoA | 3-hydroxy-3-methylglutaryl coenzyme A |
| HPV | human papillomavirus |
| HR | hazard ratio; heart rate |
| HRQOL | health-related quality of life |
| HRT | hormone replacement therapy |
| HSG | hysterosalpingogram |
| HSV | herpes simplex virus |
| HTN | hypertension |
| HVF | Humphrey visual field |
| HVPG | hepatic venous pressure gradient |
| HZV | herpes zoster virus |
| IBR | implant-based reconstruction |

| | |
|-------|---|
| ICA | internal carotid artery |
| ICD | implantable cardioverter–defibrillator |
| ICP | intracranial pressure |
| ICS | inhaled corticosteroid |
| ICU | intensive care unit |
| IDH1 | isocitrate dehydrogenase 1 |
| IFN | interferon |
| Ig | immunoglobulin |
| IGF-1 | insulin-like growth factor-1 |
| IHC | immunohistochemistry |
| IIEF | International Index of Erectile Function |
| IL | interleukin |
| IM | intramuscular |
| IMA | internal mammary artery |
| INR | international normalized ratio |
| IOP | intraocular pressure |
| IPD | individual patient data |
| IPI | International Prognostic Index |
| IPSS | International Prognostic Scoring System |
| IPT | interpersonal psychotherapy |
| IQR | interquartile range |
| IRIS | immune reconstitution inflammatory syndrome |
| ISN | International Society of Nephrology |
| ISS | injury severity score |
| ITT | intention to treat |
| IU | international unit |
| IV | intravenous |
| IVCP | intravenous cyclophosphamide |
| IVIG | intravenous immunoglobulin |
| IVP | intravenous pyelogram |
| IVU | intravenous urography |
| KA | keratoacanthoma |
| kb | kilobase |
| kcal | kilocalorie |
| kg | kilogram |

| | |
|--------|--|
| kPa | kilopascal |
| KPS | Karnofsky performance score |
| KUB | kidney, ureter, and bladder |
| L | litre |
| LA | local anaesthesia |
| LABA | long-acting β_2 agonist |
| LAD | left axis deviation |
| LAR | long-acting repeatable |
| LARS | laparoscopic antireflux surgery |
| LASIK | laser-assisted <i>in situ</i> keratomileusis |
| LDL | low-density lipoprotein |
| L-dopa | levodopa |
| LGG | low-grade glioma |
| LH | luteinizing hormone |
| LHRH | luteinizing hormone-releasing hormone |
| LMWH | low-molecular-weight heparin |
| LN | lupus nephritis |
| LPR | laryngopharyngeal reflux |
| LR | likelihood ratio |
| LTG | lamotrigine |
| LTOT | long-term oxygen therapy |
| LUTS | lower urinary tract symptoms |
| LV | left ventricular |
| LVEF | left ventricular ejection fraction |
| LVRS | lung volume reduction surgery |
| m | metre |
| MACCE | major adverse cardiac and cerebrovascular events |
| MADRS | Montgomery and Asberg Depression Rating Scale |
| MAP | mean arterial pressure |
| MCI | mild cognitive impairment |
| MDI | multiple daily injection; metered dose inhaler |
| MDR | multidrug resistance |
| MDS | myelodysplastic syndrome |
| MeSH | medical subject heading |
| mg | milligram |

| | |
|-------|--|
| MGMT | O-6-methylguanine DNA methyltransferase |
| MI | myocardial infarction |
| MIC | minimal inhibitory concentration |
| min | minute |
| mIU | million international unit; milli international unit |
| MJ | megajoule |
| mL | millilitre |
| mm | millimetre |
| MMA | maxillomandibular advancement |
| MMC | mitomycin C |
| MMF | mycophenolate mofetil |
| mmHg | millimetre of mercury |
| mmol | millimole |
| MMS | Mohs' micrographic surgery |
| MMSE | Mini-Mental State Examination |
| MNG | multinodular goitre |
| mo | month |
| MOD | multiple organ dysfunction |
| MRA | magnetic resonance angiography |
| MRC | Medical Research Council |
| MRI | magnetic resonance imaging |
| ms | millisecond |
| MS | multiple sclerosis |
| mTOR | mammalian target of rapamycin |
| MTX | methotrexate |
| MU | million units |
| MUGA | multiple-gated acquisition |
| mV | millivolt |
| MVR | mitral valve replacement |
| 6MWD | 6-minute walking distance |
| MWT | maintenance of wakefulness test |
| NAC | <i>N</i> -acetylcysteine |
| nAMD | neovascular age-related macular degeneration |
| NAPSI | nail psoriasis severity index |
| nCPAP | nasal continuous positive airways pressure |

| | |
|------------------|--|
| NEC | necrotizing enterocolitis |
| ng | nanogram |
| NHL | non-Hodgkin's lymphoma |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NICHHD | National Institute of Child Health and Human Development |
| NICU | neonatal intensive care unit |
| NIH | National Institute of Health |
| NIHSS | National Institutes of Health Stroke Scale |
| NIPPV | non-invasive positive pressure ventilation |
| NIV | non-invasive ventilation |
| nmol | nanomole |
| NNH | number needed to harm |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NNT | number needed to treat |
| NICE | National Institute for Health and Care Excellence |
| NMBA | neuromuscular-blocking agent |
| nmol | nanomole |
| NO | nitric oxide |
| N ₂ O | nitrous oxide |
| NOAC | novel oral anticoagulant |
| NOSIE-30 | Nurses' Observation Scale for Inpatient Evaluation |
| NPH | Neutral Protamine Hagedorn |
| NPI | NeuroPsychiatric Inventory |
| NPV | negative predictive value |
| NRT | nicotine replacement therapy |
| NRTI | nucleoside reverse transcriptase inhibitor |
| ns | not significant |
| NSABP | National Surgical and Adjuvant Breast Project |
| NSAID | non-steroidal anti-inflammatory drug |
| NSCLC | non-small cell lung cancer |
| NSTEMI | non-ST-elevation myocardial infarction |
| NTx | N-telopeptide |
| NYHA | New York Heart Association |

| | |
|---------------------|--|
| O ₂ | oxygen |
| OA | osteoarthritis |
| OAI | Obstructive Apnoea Index |
| OBT | optimized background therapy |
| OCT | optical coherence tomography |
| od | <i>omni die</i> (once daily) |
| ODI | Oswestry disability index |
| OEF | oxygen extraction fraction |
| OHT | ocular hypertension |
| OME | otitis media with effusion |
| OR | odds ratio |
| OSA | obstructive sleep apnoea |
| OSAHS | obstructive sleep apnoea hypopnoea syndrome |
| O ₂ sats | oxygen saturation |
| PAC | pulmonary artery catheter |
| PaCO ₂ | arterial pressure of carbon dioxide |
| PANSS | Positive and Negative Syndrome Scale |
| PaO ₂ | arterial pressure of oxygen |
| PAP | pulmonary artery pressure |
| PASI | psoriasis area severity index |
| PC-BPPV | posterior canal benign paroxysmal positional vertigo |
| PCI | percutaneous coronary intervention |
| PCNL | percutaneous nephrolithotomy |
| PCOS | polycystic ovarian syndrome |
| PCR | polymerase chain reaction |
| PD | Parkinson's disease |
| PDE | phosphodiesterase |
| PE | pulmonary embolism; plasma exchange |
| PEF | peak expiratory flow |
| PEG-IFN | pegylated interferon |
| PET | positron emission tomography |
| PFS | progression-free survival |
| pg | picogram |
| PGA | physician's global assessment |
| PGIC | Patient Global Impression of Change |

| | |
|------------|--|
| PI | protease inhibitor |
| PID | pelvic inflammatory disease |
| p.m. | <i>post meridiem</i> (after noon) |
| PM | post-mortem |
| pmol | picomole |
| PO | <i>per os</i> (by mouth) |
| POAG | primary open-angle glaucoma |
| POEM | patient-orientated eczema measurement |
| pOME | persistent otitis media with effusion |
| POMS | Profile of Mood States |
| PONV | post-operative nausea and vomiting |
| PPCI | primary percutaneous coronary intervention |
| PPI | proton pump inhibitor |
| ppm | part per million |
| pPROM | preterm, prelabour rupture of membranes |
| PPV | positive predictive value |
| PR | progesterone receptor |
| PRA | plasma renin activity; panel-reactive antibody |
| PRAM | preschool respiratory assessment measure |
| PRK | photorefractive keratectomy |
| PROM | patient-reported outcome measure; prelabour rupture of membranes |
| PRP | pan-retinal photocoagulation |
| PSA | prostate-specific antigen |
| PTCA | percutaneous transluminal coronary angioplasty |
| PTH | parathyroid hormone |
| PUJ | pelvi-ureteric junction |
| PUVA | psoralen UVA |
| QALY | quality-adjusted life-year |
| qds | <i>quater die sumendus</i> (four times daily) |
| Q_{\max} | maximum urinary flow rate |
| QoL | quality of life |
| RA | rheumatoid arthritis |
| RAEB | refractory anaemia with excess blasts |
| RAI | radioactive iodine |

| | |
|-------------------|--|
| RBC | red blood cell |
| RCC | renal cell carcinoma |
| R-CHOP | rituximab and CHOP |
| RCM | red cell mass |
| RCOG | Royal College of Obstetricians and Gynaecologists |
| RCT | randomized controlled trial |
| RD | risk difference |
| RDS | respiratory distress syndrome |
| REAL | Revised European American Classification of Lymphoid Neoplasms |
| RFA | radiofrequency ablation |
| RNA | ribonucleic acid |
| ROSC | return of spontaneous circulation |
| RPA | recursive partitioning analysis |
| RPR | rapid plasma reagin |
| RPS | Renal Pathology Society |
| RR | relative risk; respiratory rate |
| RRR | relative risk reduction |
| RRT | renal replacement therapy |
| RSA | radiostereometric analysis |
| RT | radiotherapy |
| r-tpa | recombinant tissue plasminogen activator |
| RUD | Resource Utilisation in Dementia |
| RV | residual volume |
| s | second |
| SAH | subarachnoid haemorrhage |
| SaO ₂ | arterial oxygen saturation |
| SAT | spontaneous awakening trial |
| SBI | Sciatica Bothersomeness Index |
| SBP | systolic blood pressure |
| SBT | spontaneous breathing trial |
| SC | subcutaneous |
| SCC | squamous cell carcinoma |
| SCORAD | SCORing Atopic Dermatitis |
| SCVO ₂ | central venous oxygen saturation |

| | |
|-----------|--|
| SD | standard deviation |
| SE | side effect; standard error |
| SERM | selective oestrogen receptor modulator |
| SF36 | Short Form-36 |
| SF-36 PF | Short Form-36 Physical Function |
| SF-36 QoL | Short-form 36 Quality of Life Questionnaire |
| SFA | superficial femoral artery |
| SF-MPQ | Short Form McGill Pain Questionnaire |
| SFRR | seizure-free retention rate |
| SGRQ | St George's Respiratory Questionnaire |
| SIB | Severe Impairment Battery |
| SIDS | sudden infant death syndrome |
| SIGN | Scottish Intercollegiate Guidelines Network |
| SIRS | systemic inflammatory response syndrome |
| SLE | systemic lupus erythematosus |
| SMC | specialist medical care |
| SNRI | serotonin/norepinephrine reuptake inhibitor |
| SNRS | Scripps Neurological Rating Scale |
| SP | supportive psychotherapy |
| SRS | stereotactic radiosurgery |
| SS | surgical stripping |
| SSIH | spontaneous supratentorial intracerebral haemorrhage |
| SS-QOL | stroke-specific quality of life |
| SSRI | selective serotonin reuptake inhibitor |
| STD | sexually transmitted disease |
| STEMI | ST-elevation myocardial infarction |
| STN | subthalamic nucleus |
| STS | Society of Thoracic Surgeons |
| SVR | sustained virological response |
| TAD | tip–apex distance |
| TAVI | transcatheter aortic valve implantation |
| TB | tuberculosis |
| TBM | tuberculous meningitis |
| TBSA | total burn surface area |

| | |
|-------|---|
| TCA | tricyclic antidepressant |
| TCC | transitional cell carcinoma |
| TDI | transition dyspnoea index |
| T1DM | type 1 diabetes |
| T2DM | type 2 diabetes |
| tds | <i>ter die sumendus</i> (three times daily) |
| THA | total hip arthroplasty |
| TIA | transient ischaemic attack |
| TKI | tyrosine kinase inhibitor |
| TKR | total knee replacement |
| TLC | total lung capacity |
| TLE | temporal-lobe epilepsy |
| TME | total mesorectal excision |
| TNF | tumour necrosis factor |
| TPMT | thiopurine methyltransferase |
| TUR | transurethral resection |
| TURBT | transurethral resection of bladder tumour |
| TURP | transurethral resection of the prostate |
| TVT | tension-free vaginal tape |
| U | unit |
| UC | ulcerative colitis |
| UCVA | uncorrected visual acuity |
| UFH | unfractionated heparin |
| UK | United Kingdom |
| UKPDS | UK Prospective Diabetes Study |
| UKR | unicompartmental knee replacement |
| uPCR | urine protein/creatinine ratio |
| UPDRS | Unified Parkinson's Disease Rating Scale |
| URS | ureterorenoscopy |
| URTI | upper respiratory tract infection |
| US | ultrasonography; ultrasound |
| USA | United States of America |
| USS | ultrasonography |
| UTI | urinary tract infection |
| UVA | ultraviolet A |

| | |
|------|--|
| UVB | ultraviolet B |
| VA | visual acuity |
| VAC | vacuum-assisted closure |
| VACV | valaciclovir |
| VAS | visual analogue score |
| VCSS | Venous Clinical Severity Score |
| VD | venereal disease |
| VEGF | vascular endothelial growth factor |
| VF | ventricular fibrillation; visual field |
| VL | viral load |
| VLDL | very low-density lipoprotein |
| VLP | virus-like particle |
| V/Q | ventilation–perfusion |
| VR | vestibular rehabilitation |
| vs | versus |
| VT | ventricular tachycardia |
| VTE | venous thromboembolism |
| VV | varicose vein |
| WBC | white blood cell |
| WBRT | whole-brain radiation therapy |
| WCC | white cell count |
| WHO | World Health Organization |
| wk | week |
| y | year |

How to use this book

Introduction

With growing emphasis on evidence-based medicine (EBM), there is a need for all health-care professionals to be aware of the important evidence that shapes their clinical practice. While several sources (ranging from Internet databases to journals) exist to house the vast number of articles published every day, approaching these can be daunting. For the uninitiated, literature searching is a tiresome and complex process, especially as it can be difficult to determine which studies are significant and clinically relevant, without prerequisite specialist knowledge. Furthermore, even if the reader is aware of the importance of a particular study, navigating the complexities of its methodology and accurately evaluating its results to arrive at the correct conclusions can be an equally frustrating task. In the modern era, time constraints make this an even greater challenge, leaving many just 'reading the abstract' and, at times, inappropriately applying the authors' conclusions into their clinical practice.

This book has been written by experts in each specialty to provide a simple and fast search tool for locating relevant key clinical evidence. A brief critique of the important and salient points of each trial is also provided. This serves as a 'rapid learning aid' for those who want to understand more about the landmark clinical trials in a specialty, without having to trawl through vast amounts of material. There will be those who gasp in horror at this unashamedly simple stripping down of evidence. Others may question the selection of certain studies. However, making EBM amenable to all requires a degree of ruthlessness in the selection and presentation of trials and their data. We hope that the reader will gain an understanding of the underlying process behind EBM through analysis of the trial methodologies and outcomes of the notable studies considered in this book, allowing future research to be conducted and scrutinized at a similarly high level.

Layout and formatting

This book is divided into four sections: introductory chapters on the history and fundamentals of evidence-based medicine, medical specialties, paediatrics and surgical specialties. Individual chapters contain landmark trials that have influenced practice in that specialty, and are subdivided according to conventional disease groupings. Allocation of trials to individual chapters has not been an easy task, in particular due to considerable overlap between topics. Thus, although we have grouped similarly themed trials where possible, in some cases topics have been placed within the specialty most relevant to daily clinical practice (e.g. deep vein thrombosis in Emergency Medicine).

In order to maintain consistency, we have applied a broadly standardized two-page template for the analysis of individual trials. Spellings follow either the original trial or OUP house style, with internationally agreed nomenclature whenever multiple variations have arisen (e.g. names of drugs). Country of origin-specific references, e.g. to the UK's National Institute

for Health and Care Excellence (NICE) or Royal Colleges, have only been included, when necessary, to convey the impact of a study.

Trial selection

In a book of this nature, the personal preferences of our expert contributors are inherent in the selection of studies. However, in order to ensure a consistent approach and to minimize selection bias, we presented several criteria:

- Need for impact: a paper must have made (or must have the future potential to make) a significant impact on clinical practice;
- Important topics: trials should relate to the key issues/diseases in the specialty, and not to more esoteric and/or less clinically relevant topics, particularly those less relevant to non-specialist audiences;
- Sound methodology: level 1b evidence (randomized controlled trials (RCTs) from peer-reviewed journals), whenever possible. Lower-quality evidence permitted if it is influential;
- Number of trials: maximum of 25 trials per chapter (with some understandable variation between different specialties);
- Discussion with peers: authors were requested to consult with colleagues when selecting and interpreting trials.

It is important to note that this book is not intended to be a collection of evidence-based protocols for guiding all aspects of clinical management; textbooks, such as the *Oxford Handbook of Clinical Medicine*, already serve this purpose. Furthermore, with the aim of focusing upon therapeutic intervention, there are a number of notable exclusions. These include stand-alone scientific discoveries (the discovery of penicillin did not come about as a result of a methodologically sound trial!), epidemiological associations (e.g. Sir Richard Doll's pioneering work establishing the relationship between smoking and lung cancer), and scoring systems/severity criteria (e.g. development of Wells' criteria for deep vein thrombosis or the CURB-65 prognostic score for pneumonia).

The primary focus of this book is the RCT. There are several other important resources that focus on meta-analysis, as it is these that largely drive treatment decisions. However, with meta-analyses relying upon high-quality RCTs to drive them, the increasing focus often placed upon level 1a evidence can often leave the RCT to fall by the wayside. RCTs with rigorous methodology that are sufficiently powered to detect statistical differences in clearly defined outcomes are vital in ensuring bias limitation and appropriate application of evidence to practice. This book serves as a 'Who's Who' of those RCTs that have stood the test of scrutiny and time and have led to an evidence-based change in clinical practice. These trials are presented with a brief discussion of a much wider context; isolated application of the result of individual RCTs to clinical practice is not recommended. For a treatment-related approach to clinical evidence, resources, such as the Cochrane Collaboration and the *BMJ's Clinical Evidence* are to be commended for bringing EBM from the academic to the clinician. Direct applicability of evidence to diagnostic and therapeutic practices is increasingly supported by excellent guidelines from national bodies, e.g. the American Heart Association or the British Thoracic Society. In the UK,

evidence-based ‘best practice’ guidelines are also presented by the various Royal Colleges. However, overcoming financial hurdles and time constraints is often required, before these translate to the guidelines recommended by individual centres.

Although our contributors have had the entirety of the vast clinical literature from which to select their trials (over 3,000 medical journals exist with over 17 million citations on Medline), it is no surprise that a considerable number of those featured in this book hail from journals such as *The Lancet*, *New England Journal of Medicine*, *JAMA*, or the *BMJ*. It is possible that their wide readership and high impact factor (a measure based upon citations, first proposed in the 1960s) have in themselves led to a selection bias, both for the purposes of this book as well as for literature reviews undertaken beyond the confines of this text. This places an important responsibility upon the shoulders of their editors with regard to the maintenance of high standards. Interestingly, although citations are a useful tool for tracking the progress of research, studies have shown little correlation between highly cited papers and their ranking by experts decades later, perhaps due to poor papers being cited repeatedly for their notorious flaws. Extrapolation of clinical evidence to clinical practice must therefore be undertaken with care and only applied to relevant populations; independent reviews of the results, alongside the various indices for rating the quality and strength of evidence-based recommendations (e.g. GRADE system), are helpful practical tools.

Limitations

Recognition of the remit and limitation of a study is an important attribute to be considered when interpreting its results. In this regard, our book is no exception, with some understandable limitations of its own. Foremost, perhaps, is space; we have, at times, had to be somewhat brutal in our selection of trials, in order to allow space for the range of specialties encompassed within this book. This is therefore far from an exhaustive selection of all the important trials that exist in the literature. Furthermore, studies are usually reported as medium-length articles in the medical literature (typically around 3,000–4,000 words); this book only provides a two-page summary of each paper, not the complete picture.

Our many contributors have provided their interpretation of published data in good faith and in keeping with their understanding of best practice within their specialty. However, the medical literature is not perfect. At times, the quality of evidence is limited through no fault of the researchers. This is particularly the case for some surgical topics where RCTs cannot always be conducted and may sometimes be inappropriate. Therefore, the onus is on all evidence-based practitioners to critically appraise the available literature. Clinical research is not infallible, and errors of judgement are often made. The correction of errors and the withdrawal of both papers themselves and the therapeutic agents they test are not unheard of.

Evidence is nothing without its interpretation in the appropriate context. We therefore recommend that readers who wish to consider the results of individual studies use the analysis in the book not in isolation, but as an adjunct to the original literature. The summaries will highlight the key aspects of the findings, while the original papers will provide a fuller

understanding of the context and any further analysis/limitations. The interpretation of medical statistics is an art, as well as a science. This is often the aspect of EBM that frightens most casual observers; in this regard, the statistical significance of the results presented in this book has been presented in a simplified form for clarity. Readers should consider the summaries in conjunction with the more detailed statistical analysis presented in the original paper. In an era of cost-cutting, the financial implications of any findings should also be considered.

Of final note is an understandable concern that the book could rapidly become out of date. While there may have been some important studies published between editing and publication, we feel that our selection criterion requiring a study to have made notable impact upon practice will have minimized this; while new research emerges daily, only a very small percentage achieves landmark status. Indeed, it is often only several years later that the relative clinical importance of a trial becomes established.

What makes a good study?

Our other introductory chapters answer this question from a more historical and technical perspective. However, after review of the 1,000+ trials considered for this book, a number of more basic attributes have emerged that make the study of EBM considerably more palatable from a reader's perspective. In particular, we applaud those that exude intrinsic simplicity from the outset, e.g. by using consistency of layout; and straightforward and concise wording to explain concepts; and clear diagrams, tables, and flow charts to show participant progression and results. Furthermore, all data must be accounted for; e.g. the reasons for participant withdrawal must be explicitly stated. Perplexing one's readers is not a mark of scientific prowess, and it is surprising how many studies have chosen to hide their findings behind a guise of complexity. One wonders whether this is in order to mask poor methodology or simply due to poor author understanding. It is precisely this unnecessary complexity and poor presentation that makes EBM an unapproachable subject for many. The editorial efforts of leading journals to standardize and simplify their formats have been a welcome stride in incorporating EBM into everyday practice. It is our hope that this book will take this process a step further.

With a need to focus on the methodology of individual studies, and through space constraints, we have made limited consideration of the ethical and conflict of interest issues that surround scientific research. Consent and ethical approval are key areas that must underlie all research, the principles of which are now established in various international guidelines (Nuremberg code, Declaration of Helsinki), as well as through the work of various bodies (e.g. UK's Nuffield Council on Bioethics). Despite guidelines, some claim that research conveying favourable outcomes (particularly when influenced by those with a conflict of interest, such as association with a pharmaceutical company) is more likely to be published than a study reporting negative findings. Furthermore, there is not always correlation between the actual results of trials/meta-analysis and the conclusions drawn by the authors. The source of such bias is unclear but must be overcome. Similarly, a solution is not easy; restriction of corporate funding may lead to a significant decrease in research activity.

Controversy is inherent to scientific study, and both the media and researchers have a moral obligation to ensure that the public are reminded that snippets of discussion do not necessarily translate to straightforward conclusions. Deliberate reporting of misleading and biased information in order to produce attention-grabbing headlines is a dangerous game and serves only to yield unrealistic expectations; public scandals should not deter research. The studies presented in this book serve as a reminder of the overall victory of balanced scientific endeavour and of the evolving practice of EBM.

Part 1

Introduction

The history of evidence-based medicine

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|--|----|
| The nature of evidence | 4 |
| Making comparisons | 6 |
| The first prospective controlled trial | 8 |
| The enlightenment | 9 |
| The importance of case studies | 10 |
| The nineteenth century | 11 |
| Statistical developments | 12 |
| Of placebos and the mind in eighteenth- and nineteenth-century healing | 16 |
| Problems of design: the clinical trial in the nineteenth and twentieth centuries | 18 |
| The rise of the randomized controlled trial | 22 |
| Ethics and experimentation | 26 |
| Chronology | 30 |

The nature of evidence

‘The words of a dialectician are like a spider’s web: of no practical value but a triumph of ingenuity’ (Aristotle)

The pursuit of tests for therapeutic interventions has been a characteristic of Western medicine since ancient times. Whereas Eastern medical systems centred on wisdom and tradition, the West centred on the known, how it was constituted (methodology), and expertise. The ‘stasis’ of Chinese and Hindu medical systems reflected the civil and moral orders of their respective cosmologies. However, ‘physis’, the Greek for ‘nature’ or ‘change’ from which we get the term ‘physics’, reflected the West’s.¹

Nature could be in hiding or personify the essence of things, as in the veiled Egyptian goddess Isis, or the Roman goddess of Nature Diana. In a world of constant change, the veil of Isis could be lifted or Diana’s secrets discovered by the arts (‘techne’) and sciences.²

Such attitudes towards Nature characterized the founding of modern experimental science in the seventeenth century in which Nature was a laboratory and could be brought to court, interrogated, and, if necessary, tortured. However, during the Romantic era, an opposing vision of Nature arose. Nature had her secrets, but she was not veiled. The shutters were in our eyes for not seeing Nature outright.

Overview of the history of clinical trials

Historical accounts of the clinical trial are usually expressed through the lens of presentism: how the various components of the first modern randomized controlled trial (RCT)—the comparison, blinding, and randomization—culminated in Austin Bradford Hill’s 1946 trial of streptomycin for tuberculosis (TB). Accounts include: the first references to comparative approaches; therapeutic assessments, e.g. (rich vs plain diet in the Bible); James Lind’s eighteenth-century controlled trial of the citrus fruit for scurvy; the recognition of the importance of suggestion or confidence in the treatment effect in both patient and practitioner, with subsequent adoption of blinding and placebos in trials of animal magnetism and homeopathy in the eighteenth and nineteenth centuries; and later quantification and randomization to remove bias in the nineteenth and twentieth centuries.³

The factual context of the development of the RCT is important, if only to emphasize the historicity of contemporary research methodology. However, the adoption of the various components of the trial at any one time has as much to do with changing socio-political and ethical contexts as the ‘objective’ scientific standards of evidence. Evidence is not just scientific data floating in some ethereal medium, but is linked to facts and beliefs of the various members of diverse medical communities who interpret evidence and deploy it to legitimize various strategies.

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Making comparisons

From physic to medicine

The terms 'physic' and 'medicine' denote two separate traditions in medicine: one based on learning and preservation of health, the other based on experience and curing.⁴

The ancient notion of 'physic' (meaning 'nature') characterized the physician's art. The aim was to advise right living in accordance with nature, based upon Galen's humoral principles of blood, phlegm, and black and yellow bile. A balance of these denoted health, and an imbalance 'dyscrasis' (ill health). The focus was on regulating the six non-naturals—food and drink, the environment, evacuations, sleep, exercise, and state of mind—in order to maintain natural body balance. Herbal concoctions and bloodletting practices restored the humoral imbalance. Ancient pharmacology could boast some 760 medicinal plants and herbs, as well as rules to adjudicate their effectiveness. A drug needed to be pure and work in all cases of the disease, with its effectiveness corresponding to the dose and strength. Testing a drug's effectiveness in humans under different conditions was a 'final trial'.⁵

'Medico', derived from the Latin 'to drug' or 'dye', emphasized the ability to treat disease with drugs. Its adoption coincided with the rise of the new experimental philosophy in the seventeenth century associated with Isaac Newton, Robert Boyle, Francis Bacon, and René Descartes.

New remedies, such as the cinchona bark from South America and the new chemical remedies introduced earlier by Paracelsus (including mercury, arsenic, iron, lead, and sulfur), challenged traditional medicine. William Withering's discovery of foxglove (*digitalis*) for dropsy and Edward Jenner's vaccination against smallpox in the eighteenth century reinforced the curative aspect of medicine. Indeed, in his utopian fantasy *New Atlantis* (1627), were not Francis Bacon's 'Compilers' and 'Lamps' the forerunners of the United Kingdom (UK)'s National Institute for Health and Care Excellence (NICE)? He wrote:

'We have three [practitioners] that draw the experiments of the former four [the 'Pioneers' or 'Miners'] into titles and tables to give better light for the drawing of observations and axioms out of them [and] Lamps [who] direct new experiments of a higher light.'

Primacy of clinical experience

What was crucial to good practice in both traditions was 'clinical experience'—whether using countless remedies associated with 'empirics', or those conforming to Galen's experiences. The great Muslim physician, Rhazes (AD 865–925) believed the experience of one wise doctor was worth more than all of what was written in books:

'So when you see these symptoms, then proceed with bloodletting. For I once saved one group [of patients] by it, while I intentionally neglected [to bleed] another group. By doing that, I wished to reach a conclusion.'

Making comparisons was essential to assessing the efficacy of treatment. In his 1364 'Letter to Bocaccio', the humanist Petrarch went one step further in his critique of Galenic depletive remedies:

'I solemnly affirm and believe, if a hundred or a thousand men of the same age, same temperament and habits, together with the same surroundings, were

attacked at the same time by the same disease, that if one half followed the prescriptions of the doctors of the variety of those practising at the present day, and that the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape.'

The first reference to randomization

Several hundred years later, in 1662, the iatrochemist JB Van Helmont upped the rhetorical stakes in attacks on orthodox medicine, urging the use of lots in order to make fair comparisons:

'Let us take out of the Hospitals... 200 or 500 poor People, that have Fevers, Pleurisies, etc. Let us divide them in halves, let us cast lots, that one half of them may fall to my share, and the other to yours; I will cure them without bloodletting and sensible evacuation; but do as you do, as ye know (for neither do I tie you up to the boasting, or of Phlebotomy, or the abstinence from a solutive Medicine) we shall see how many Funerals both of us shall have.'

The outcomes of lotteries or the roll of dice were keenly debated by Puritan divines in the seventeenth century; were they direct signs of God's will or determined by natural law? Van Helmont's use of lots ensured that bias was avoided in assembling the two groups. Whether he actually meant to conduct the experiment remains debatable.

Ambrose Paré: comparison in surgery

With the shift in emphasis to the curative component of medicine, surgeons too eschewed old practices and put their faith in personal observation and experience. The renowned French surgeon Ambrose Paré made this within patient comparison in 1575:

'A German guard was very drunk and his flask caught fire and caused great damage to his hands and face, and I was called to dress him. I applied onions to one half of his face and the usual remedies to the other. At the second dressing I found the side where I had applied the onions to have no blisters nor scarring and the other side to be all blistered.'

More famously, Paré determined that the use of cautery was otiose to the outcome of gunshot wounds—much to the relief of the victims:

'At last I ran out of oil and was constrained to apply a digestive made of egg yolk, oil of roses and turpentine. That night I could not sleep easily thinking that by the default in cautery I would find the wounded to whom I had failed to apply the said oil dead of poisoning; and this made me get up at first light to visit them. Beyond my hopes I found those on whom I had put the digestive dressing feeling little pain from their wounds, which were not swollen or inflamed, and having spent quite a restful night. But the others, to whom the said oil had been applied, I found fevered, with great pain and swelling around their wounds.'

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The first prospective controlled trial

In 1747, the naval surgeon James Lind used comparative groups to assess the correct treatment for scurvy, while on board his ship the *Salisbury*. He published his *'A treatise on the scurvy'* in 1753 and is rightly considered to be the pioneer of the first prospective controlled clinical trial.

Scurvy was considered to be a putrid disease of the blood, associated with moist air that blocked perspiration, and had long plagued long sea voyages. The practice of doling out citrus fruit as an anti-inflammatory potion had been adopted by the Portuguese since the sixteenth century. Sir Captain James Lancaster, working for the East India Co., conducted a quasi-controlled trial as early as 1601, when the diet of one of the four ships under his command was supplemented with two teaspoons of lemon juice. It seems unlikely that this was a deliberately designed experiment—rather a situation forced by a shortage of supplies, in the tradition of Paré. Towards completion of the journey, it was noted:

*'Very many of our men were fallen sicke of the scurvey in all our ships and unlesse it were in the generals ship only, the other three were so weake of men that they could hardly handle the sayles.'*⁶

The three ships had acted as unintentional controls.

James Lind was well aware of the literature on scurvy, when he published his own investigations. He had, in fact, conducted a systematic review. The trial was deliberately prospective in assessing the merits of six treatments:

*'I took twelve patients... Their cases were as similar as I could have them. They... had putrid gums, the spots and lassitude, with weakness of the knees... They had one diet common to all... Two of them were ordered each a quarter of cider a day, Two others took twenty-five gutts of elixir of vitriol, three times a day, Two others took spoonfuls of vinegar, three times a day... Two of the worst patients were put under a course of sea water... Two others had had each two oranges and one lemon... They continued but six days under this course... The two remaining patients took... nutmeg... and an electuary... and purged three times a-day.'*⁷

The pair given the citrus fruit were fit for duty 6 days later and put to taking care of the others who remained sick. In the face of good evidence about the effectiveness of oranges and lemons in scurvy, why did it take some 43 years before the Navy Board regularly stocked the ships with citrus fruit? The uncertain explanation of scurvy certainly played a role in its slow uptake, allowing other remedies, such as 'McBride's malt wort' and sauerkraut, to be given equal consideration. Cumulative clinical experience and numerical record-keeping in the fleet and in its hospitals during the ensuing decades allowed the clinical features of scurvy and its treatment to be better assessed. Largely through the efforts of Sir Gilbert Blane, the general issue of lemon juice finally occurred in 1795.

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The enlightenment

Smallpox and the arithmetic tradition

An analytical approach to assessing interventions in the eighteenth century was taken up by the inoculators of smallpox. They stood in line with the arithmetic tradition that stemmed from numerical analysis of the London Bills of Mortality; this was initiated in the seventeenth century by two London tradesmen who created the notion of 'political arithmetic' or social statistics. Such bills set out the numbers and causes of death in each parish. A century later, innovative inoculators, such as the Yorkshire doctor Thomas Nettleton, published calculations of ratios of mortality to morbidity and inoculated smallpox in a number of towns. For the preceding year, Nettleton recorded a total of 3,405 cases, with 636 deaths. The 18.8% mortality rate was compared to 0% for the inoculated groups!⁸

The Near and Far Eastern practice of inoculation had been introduced by Lady Mary Montagu and others a decade or so earlier. It was the first widespread intervention not only to inspire numerical assessments, but also to raise widespread concerns about safety and efficacy. Human experimentation was the test of choice. Persuaded by his daughter Caroline, Princess of Wales, George I agreed to pardon six convicts in Newgate Prison if they agreed to volunteer for a trial of inoculation. Three men were matched with three women for age. All six survived and were subsequently pardoned. As a quasi-test of efficacy, Maitland, the doctor in charge, also arranged for one of the inoculated women in the trial to sleep next to a young smallpox victim. After 6 weeks of exposure, she had not fallen sick.

Smallpox inoculation became widespread by the 1750s, largely due to Princess Caroline having had her own children inoculated. However, much religious opposition accompanied the practice. From today's perspective, the data collected by Nettleton and others were imperfect, as they did not know the exposure period or the rate of the inoculated patients. Given the high incidence of natural smallpox in the eighteenth century, efficacy did seem to have been reasonably well established, and the data gathered did represent numerical evidence for the efficacy of inoculation.⁹

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The importance of case studies

The reporting of individual case studies characterized much of eighteenth-century medical literature, in which new procedures and cures were introduced to an increasingly consumer-focused medical marketplace. William Withering was exceptional in resisting the pressures of the market and rushing to publish his first successes of treating dropsy with foxglove (*digitalis*). Caution prevailed, until he had assembled enough evidence—156 cases over a 10-year period; in 1785, he wrote:

‘It would have been an easy task to have given select cases, whose successful treatment would have spoken strongly in favour of the medicine, and perhaps been flattering to my own reputation. But Truth and Science would condemn the procedure. I have therefore mentioned every case . . . proper or improper, successful or otherwise.’

With equal circumspection, the Reverend William Stone waited 5 years to announce the results of his studies on the successful treatment of rheumatic fever with willow bark (*Salix alba*).¹⁰

Withering was aware that factors, such as age, affected the outcome of his patients treated with foxglove, but it was in the work of the surgeon William Cheselden—famous for his lithotomy operation—that a more sophisticated appreciation was realized. In an appendix to the fourth edition of *The anatomy of the human body* (1740), he wrote:

‘But what is of most consequence to be known is the ages of those who recovered, and those who died.’¹¹

He grouped his 213 patients in 10-year age groups and reported the number of deaths for each group, thus showing the substantially lower mortality among children than in adults.

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The nineteenth century

Pierre Louis and 'La méthode numérique'

The nineteenth-century Parisian physician Pierre Louis is credited as the founder of modern epidemiology by emphasizing group comparison and population thinking in therapeutic assessments.¹²

Louis's quantitative approach was based upon a form of medical empiricism called 'sensualism', developed by the eighteenth-century philosophers Condillac and Cabanis. The patron saint of this cult of observation was Hippocrates—a mythical Hippocrates that had revolted against the philosophers' hypotheses and theories. Cabanis held that true causes could never be known—only relations between objects. The work of Condorcet and Laplace on probability provided the other platform for Louis's numerical method. For Louis, facts had no value, unless they were enumerated. To test therapies, only groups of patients 'blindly selected' and undergoing different treatments (rather than individual cases) could yield sufficient evidence to adduce the significance of differential mortality rates.

In his own investigations, Louis found that bloodletting made no difference to the outcome of pneumonia, whether it was performed early or late, or whether large amounts were taken or not. In 1835, he wrote:

'What was to be done in order to know whether bloodletting had any favourable influence on pneumonitis, and the extent of that influence?

Evidently to ascertain whether, other things being equal, the patients who were bled on the first, second, third or fourth day of their illness, recovered more readily than those bled at a later period. In the same manner, it was necessary to estimate the influence of age, or, more generally, any other circumstance, on the appreciable effects of bloodletting.'

Concerning populations, he wrote:

'For example, in any particular epidemic, let us suppose five hundred of the sick, taken indiscriminately, are subjected to one kind of treatment, and five hundred others, taken in the same manner, are treated in a different mode; if the mortality is greater among the first than among the second, must we not conclude that the treatment was less appropriate, or less efficacious in the first class than in the second? It is unavoidable; for among so large a collection, similarities of conditions will necessarily be met with, and all things being equal, the conclusion will be rigorous.'

Louis did not advocate randomized allocation of the intervention in his bloodletting study. Therefore, there remains the question of whether the early and late bloodletting groups were really comparable, given the late group had already survived the early disease stages and were subsequently more likely to have a better prognosis than those receiving the intervention in the earlier acute stages of the disease.

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Statistical developments

Size matters and confidence intervals

The numerical method linked both hospital medicine and the rise of public health in the early decades of the nineteenth century and became a tool for social analysis and reform. The concept of the 'average man' was coined at the time by Adolphe Quetelet and provided a means for detached clinical judgement that only the surety of statistics could provide.

Thomas Graham Balfour's 1854 report of a clinical trial of homeopathic belladonna for scarlet fever was an early acknowledgement of the importance of sample size in the assessment of an intervention.¹³ In the Royal Military Asylum at Chelsea, Balfour conducted a trial on soldiers' orphans by giving them belladonna alternatively. He noted little difference in morbidity between those who received the belladonna (2/26) and those who did not (2/75), concluding 'the numbers are too small to justify deductions as to the prophylactic power of belladonna.' Since only four boys came down with scarlet fever, no confident conclusion could be reached, thus avoiding what today would be a 'type 2' error, i.e. assumption of no difference when one exists (a false negative).

The concept of confidence interval (CI) also arose during this period, allowing chance effects to be reduced if a range of treatment differences were calculated, within which real differences were likely to lie. The French physician Gavarret applied Poisson's probability calculation to Louis's mortality data on bloodletting and demonstrated the weakness of the numerical method. By calculating 'the limit of possible errors', one was able to judge whether a difference between two average mortality rates in two groups of patients (each group having received different treatments) represented a true difference between the treatments. It took over 100 years for Gavarret's ideas to catch on!¹⁴

Statistics and discontents

The rise of the Paris Hospital during the French revolutionary period provided fertile ground to develop a new theory of disease, in which the clinical gaze shifted from the bedside and patient self-reporting of symptoms to the correlation of symptoms with anatomico-pathological changes. Mass observation and autopsies of the poor in Parisian hospitals increasingly confirmed this ontological trend, in which disease was perceived as a real entity. Laennec used his stethoscope to observe the signs of disease, and the reification of the patient gathered momentum during the ensuing decades, as technology encroached upon the doctor–patient relationship. The rise of laboratory medicine in Germany from the 1830s hastened this trend and introduced another notion of disease—a physico-chemical process explained by the blind inexorable laws of natural science. Physiological phenomena—chemicals in the blood and urine, temperature, the ratio of red and white cells, blood pressure (BP), nerve conduction, etc.—were to be observed, measured, and defined, according to definitions of normal and abnormal.

Claude Bernard's seminal work *An introduction to the study of experimental medicine* (1865) was a paean to positivism, placing physiology among the exact sciences. In reference to his own discoveries—the concept of the 'milieu intérieur' (homeostasis), the glycogenic function of the liver, the discovery of vasomotor nerves, the action of curare, and the function of the pancreatic juices, Bernard urged a strict determinism in studying disease that focused on real and effective causes. In this regard, statistics, with its use of averages, was too conjectural and indeterministic—as if a physiologist who:

'took urine from a railroad station urinal where people of all nations passed, and who believed he could thus present an analysis of an average European urine!'

The spectre of vitalism hovered over medicine and biology in mid-century France, and, for Bernard, the future path of scientific medicine lay in 'discovering new facts, instead of trying to reduce to equations the facts which science already possesses'. Bernard provided another example of the inutility of statistics in surgery:

'A great surgeon performs operations for stone by a single method; later he makes a statistical summary of deaths and recoveries, and he concludes from these statistics that the mortality law for this operation is two out of five. Well, I say that this ratio means literally nothing scientifically and gives us no certainty in performing the next operation; for we do not know whether the next case will be among the recoveries or the deaths. What really should be done, instead of gathering facts empirically, is to study them more accurately, each in its special determinism... to discover in them the cause of mortal accidents so as to master the cause and avoid the accidents.'

Physiology thus provided the experimental foundations of scientific medicine—not the hospital wards where natural histories of pathological lesions were classified, nor at the sick bed where too many imponderables prevented strict scientific understanding of disease. Bernard's experimental method pointed the way to future pharmacological research, but few therapeutic spin-offs arose until the advent of Pasteurism, and later chemotherapy, in the latter half of the nineteenth century.

Statistics and sanitarians

In comparison to scientific medicine's promise to cure, the 'sanitary idea' had already produced dividends by the 1860s in preventing disease, especially in crowded cities. In summer of 1854, believing an outbreak of cholera was due to contaminated water supply, the London doctor John Snow urged the Parish guardians in Soho to remove the handle of the Broad Street pump. The number of cases plummeted, thus confirming his theory that cholera was due to a waterborne organism. A pioneer in medical cartography, Snow's work proved seminal in promoting public health measures to ensure healthier lives for Londoners through efficient waste disposal and clean water supplies.¹⁵

Snow's dramatic evidence contrasted sharply with Semmelweis, a Hungarian physician, who demonstrated the principle of antiseptics prior to Joseph Lister's landmark 1867 publication on the use of carbolic acid in surgery. Semmelweis, attached to the Vienna Krankenhaus (the largest maternity hospital in the world), proved that puerperal fever could be reduced in the maternity wards if medical teams washed their hands between the autopsy and delivery rooms. His evidence was based upon a retrospective, accidentally controlled trial. Between 1840 and 1846, Semmelweis noted mortality rates from childbed fever were 98/1,000 in the ward staffed by doctors and medical students, but only 36/1,000 in the ward staffed by midwives. With large numbers involved (nearly 43,000 births and some 300 deaths), he knew these findings were not due to chance. The explanation? Simple hand hygiene. As midwives did not conduct autopsies, Semmelweis insisted medical men washed their hands before examining patients on the maternity wards. The chloride of lime handwash cut the death rate to 13/1,000.¹⁶

Semmelweis was not the ideal publicist of his findings. Mentally unstable, he ended up in an asylum. He was insensitive to professional etiquette and polemic in his dealings with colleagues who viewed his major work *Etiology, concept and prophylaxis of childbed fever* (1860) as good, sound, practical advice in the sanitary tradition, but nothing extraordinary.¹⁷

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Of placebos and the mind in eighteenth- and nineteenth-century healing

Doctors had long recognized that much illness was self-limiting. Moreover, a patient's psychology was often crucial in determining therapeutic outcomes. The renowned Edinburgh physician and lecturer William Cullen gave substance to such thoughts, when he referred in his 1772 lectures to the use of placebos in medicine.¹⁸

Placebo, from the Latin 'to please', was originally used in the context of religious ritual and flattery. It metamorphosed into a medical term in Cullen's lexicon when, in prescribing a mustard plaster without any curative intent, he said:

*'I own that I did not trust much to it, but I gave it because it is necessary to give a medicine, and as what I call a placebo. If I had thought of any internal medicine it would have been a dose of the Dover's powders.'*¹⁹

For Cullen, all illness arose from irritability of the nervous system, and his promulgation of an active placebo (as compared with a more familiar inert one such as a bread pill) to please a difficult patient showed how such notions as 'sympathy' and 'vitalism' informed his mind-body therapeutics and psychosomatic theory of illness.

Testing mesmerism

The idea of inducing a hypnotic trance in patients by the action of a universal fluid 'animal magnetism' was called mesmerism after the famous Viennese physician Franz Anton Mesmer. He stood accused in 1780 of making fraudulent claims about his discovery of animal magnetism and its therapeutic effects. In a series of trials undertaken by members of the Academy of Sciences and Medicine, women were blindfolded and asked to either locate the source of the 'mesmerism' or were deceived into thinking they were subject to mesmeric influences when this was not the case. In others, sham or decoy assessments were part of the investigations, in which trees were mesmerized or plain water was used. All tests revealed that unblinding removed the effects and that the evinced effects were due to the imagination.²⁰

One trial proposed by the Mesmerists, yet never undertaken, seemed quite reasonable:

'24 patients are to be chosen of whom 12 will be reserved to the Faculté to be treated by the ordinary methods: the other 12 will be assigned to the Author who will treat them according to his particular method. The Author excludes from the selection all Venereal diseases.'

In the first instance, written reports will be made of the condition of each patient: each report will be signed by the Commissioners of the Faculté, by the Author and by the persons appointed by the government.

*The selection of patients will be made by the Faculté or by the Faculté and the Author together. In order to avoid any later argument and all the questions that could be raised about differences in age, in temperament, in diseases, in their symptoms etc. the assignment of the patients shall be made by the method of lots.'*²¹

The Faculty would have no truck with this early formulation of an RCT. Nevertheless, mesmerism's popularity was only temporarily blunted by the Royal Commission's negative conclusions. Throughout the nineteenth century, the magnetic movement waxed and waned.

Policing the allopathy–homeopathy boundary

Blind assessment acted as a method to police the boundaries between conventional and irregular medicine, and to guard against potential quackery. Dr John Haygarth used a sham device to investigate Perkins's tractors, small metal rods that purportedly cured all ailments through 'electrophysical force'. Five patients with rheumatism, unaware of the evaluation, were chosen from Bath General Hospital and treated with either real or wooden tractors in a cross-over study. Patients in both groups reported significant improvements. Haygarth concluded:

*'The whole effect undoubtedly depends upon the impression which can be made upon the patient's imagination.'*²²

Homeopathy particularly attracted the ire of orthodox physicians. In Trousseau's investigations at Hôtel Dieu in 1834, bread pills were used as a placebo, supposedly the first reference to the use of an inert substance. A series of ten patients were given the sham pills (there was no comparison arm using genuine homeopathic remedies), and Trousseau and his students concluded that the observed results were due solely to patient expectation. Further studies by John Forbes and the Milwaukee Academy of Medicine improved upon Trousseau's method by including a concurrent placebo and homeopathic remedy arm, as well as double-blinding of genuine homeopathic and sugar pills.

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Problems of design: the clinical trial in the nineteenth and twentieth centuries

The idea of a placebo as both an inert and physiologically active substance persisted throughout the nineteenth century. Therapeutic nihilists, like the American of heart murmur fame Austin Flint and leading Guy's Hospital physician Withey Gull, used active placebos, such as tincture of quassia or mint water, in their respective assessments of rheumatism remedies. They concluded that the conventional remedies had no effect on the natural course of the disease and that patients could get well by themselves.²³ However, in step with the growth of the pharmaceutical industry, the placebo as an inert substance gained purchase as a control in the pharmacological testing of drugs and vaccines of which 'active' molecular constituents were of central interest.

Vaccination and antisera production for typhoid, diphtheria, and other infectious diseases reached industrial proportions by the end of the nineteenth century. In Germany, Adolf Bingel performed one of the first large-scale clinical trials to assess the new diphtheria antitoxin. Between 1911 and 1914, he assigned over 900 patients alternatively to either the antitoxin serum or normal horse serum. Both patients and doctors were blinded to the intervention.²⁴

The ethics of placebos

More pragmatic concerns about how to attract patients to a no-treatment comparison arm of a trial, rather than concerns about countering suggestions, governed Anglo-American attitudes towards the adoption of blind assessment and placebos in clinical trials.²⁵ Informed consent was not an ethical norm until after World War II, and dummy treatment became a legitimate concurrent control. TB trials of sanocrysin (sodium and gold thio-sulfate) in Michigan used a single, blind assessment and distilled water as a control.²⁶

At London Hospital, a variety of 16 drugs (nitrates, narcotics, and digitalis, among them) were used in a placebo-controlled, cross-over design to assess their efficacy in the treatment of angina. No tested drug was better than placebo.²⁷

Gold's influential trial of methylxanthines for angina provided the acknowledgement that suggestion could also be the rationale behind placebo use. 'Spontaneous variation' was the usual explanation for improvements in both treatment and placebo arms. Though avoiding the word 'suggestion', Gold and his Harvard colleagues referred to 'confidence of the treatment' to explain the effects:

*'Some expressed definite conviction at times that it was the drug which was responsible for the relief. That the drug was often the lactulose placebo, and some patients insisted upon its efficacy...justifies all the circumspection one can exercise.'*²⁸

The idea that the mind and its beliefs could affect medical outcomes had been well established in the previous century. The benefits of electrotherapy, for example, in the treatment of nervous ailments, were often ascribed to the numinous quality of the latest electrical gadgetry.²⁹

Anti-quackery investigations often used sham controls.³⁰ There was growing evidence from the science of endocrinology that biology and psychology were linked. However, adoption of blind assessment was not a major feature of mainstream medicine until after World War II.

Therapeutic perspectives in the progressive era

During the interwar period, uptake of the controlled trial was determined by factors such as how dramatic the effects of the intervention were. In the 1930s, with the introduction of sulfonamides saving lives, Colebrook and colleagues at St Mary's Hospital dispensed with concurrent controls in their studies on puerperal fever, instead utilizing historical controls, i.e. comparing the mortality rates over a 4-year period, before and after the introduction of Prontosil. These were sufficient to show a convincing effect of the intervention.³¹

Where the effects of Prontosil were less obvious in the treatment of other infections, more carefully designed trials were proposed, using alternation of patients to control and treatment groups.³² Sporadic references to randomization to avoid allocation bias in clinical trials did occur, before Fisher's influential *Design of experiments* was published in 1935. In 1928, Dora Colebrook used the drawing of lots to avoid allocation bias in studying the effects of screened and unscreened ultraviolet light on schoolchildren.³³

Nevertheless, allocation through alternation remained in vogue throughout the interwar period, in spite of growing awareness of its limitations. A key milestone in methodological sophistication was reached in 1934 when Austin Bradford Hill, Professor of Medical Statistics and Epidemiology at London School of Hygiene and Tropical Medicine, criticized the Medical Research Council (MRC)'s multicentre serum therapy trial in pneumonia for its relatively small numbers and the mixture of ways in which control groups were allocated.³⁴

Hill had learned his statistics from Karl Pearson and Major Greenwood, two pioneering figures in modern statistics and epidemiology. Greenwood was the first Professor of Epidemiology and Vital Statistics at London School of Hygiene and Tropical Medicine. In his 1934 textbook *Epidemics and crowd-diseases*, Greenwood discussed the need to consider both the play of chance and differences between the individuals compared, in order to assess a treatment—in this case, vaccination.

Karl Pearson, building on the work of Francis Galton and Quetelet's earlier theory of probabilities, consolidated the discipline of biometrics and opened up the field of vital and medical statistics. Pearson grasped the significance of correlations and produced one of the first meta-analyses (the mainstay of evidence-based medicine, EBM), when asked to analyse the relative infection and mortality rates among soldiers who had volunteered for inoculation against typhoid fever and those who had not.³⁵ After

consolidating the disparate studies into one, Pearson presented tables of the observed outcomes, each study being assigned its own line showing a measure of effect. Interestingly, Pearson's analysis took issue with the effect of antityphoid vaccination, thereby delaying its widespread adoption by the army for almost a decade.

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The rise of the randomized controlled trial

AB Hill and the first randomized controlled trial

Both AB Hill and Major Greenwood were responsible for applying medical statistics to epidemiological problems of wider social significance—occupational and public health. During the interwar period, Hill's collaboration with Richard Doll on smoking was groundbreaking. Hill published widely on the topic of medicine and statistics in *The Lancet* and, in the early 1930s, grew to appreciate the benefit of randomization. Not for purely statistical reasons did he include randomization in the design of the MRC's 1946 clinical trial of streptomycin in TB—the first double-blinded RCT.³⁶

Although the importance of randomization lay in being able to stochastically measure degrees of uncertainty and variance that allowed null hypothesis testing and causal inferences to be made, evidence suggests that such important mathematical rationalizations had little to do with the MRC's design. In the 1946 study, patients with TB were randomized, using random sampling numbers and sealed envelopes, to either streptomycin and bed rest or bed rest alone.³⁷ As Hill later reflected, words like 'random samples' were left out of the protocols at that time, as they might have scared off collaborating physicians who did not want their clinical autonomy curtailed. Streptomycin was in short supply in post-war Britain, and evidence of its dramatic effects was well known. Randomization in the guise of concealed allocation was thus adopted to counter accusations of favouritism.

What turned the double-blinded RCT into a universally accepted tool was its promise of 'scientificity' by replacing clinical judgement with statistics and standardized protocols, and also taking into account the effects of bias. The placebo effect, associated with the older idea of 'suggestion' that had once been the province of the quacks, was now viewed as a confounder in medical decision-making. This appealed to the medical elite, and, by the 1960s, the RCT became a powerful tool by which organizational and social problems could be fixed. Come the early 1990s, EBM advocates held the RCT as a gold standard in medical evidence, together with the systematic review.³⁸

'All treatment must be proved to be effective'

Archie Cochrane's *Effectiveness and efficiency* (1972) was particularly influential in disseminating the gospel of the RCT in Britain.³⁹ Shaped by his wartime experiences as a prisoner of war doctor in Salonica, the book highlighted his motto 'all treatment must be proved to be effective', especially in light of the healing power of nature:

'There were about 11,000 POWs... The diet was about 600 calories per day... we all had diarrhoea. In addition we had epidemics of typhoid, diphtheria, infections, jaundice and cases of pitting oedema above the knee... We had some aspirin, some antacid and some antiseptic... I had expected 100s to die... in fact there were only 4 deaths [over 6 months]. This excellent result had nothing to do with the therapy nor my clinical skill. It demonstrated... the importance of the recuperative powers of the body.'

Pitting oedema proved to be of particular concern, as it was originally thought to be an epidemic of 'wet beriberi' caused by vitamin B deficiency.

Cochrane decided to do an experiment, in line with his medical hero James Lind:

'I chose 20 men all emaciated and with oedema above the knee. I put 10 in each of 2 wards. They all received the standard rations but those in 1 ward were given supplements of yeast, 3 times a day [paid for by himself]. In the other ward they got vitamin C. By the 4th day most of the men in the yeast room were feeling better unlike those in the vitamin C.'

The obvious inference was that the diet was improved for the prisoners. But, as Cochrane later reminisced, the quality of the trial had a lot to answer for, despite a successful outcome:

'I was testing the wrong hypothesis [now thought to be hypoproteinaemic oedema caused by famine not beriberi], the numbers too small and they were not randomised. The outcome measure was pitiful [frequency of urine output] and the trial did not go on long enough.'

Cochrane speculated that it was the protein in the yeast that did the trick. After the war, Cochrane joined the staff at the MRC Pneumoconiosis Research Unit in South Wales, later becoming Director of the MRC Epidemiology Unit in Cardiff and Professor of Medicine at the Welsh National School of Medicine. At that time, he developed interests in health service research in the National Health Service (NHS) and became an ardent proponent of the RCT.

The randomized controlled trial and discontents

Since Archie Cochrane's day, the methodological integrity of the RCT has been called into question. Concomitant with the growth of the industrial-academic-governmental complex, the RCT has proven not to be an inflexible mathematical model, but an agent subject to accommodations and compromises that serve medical and socio-economic ends. In the hands of 'Big Pharma' (the global pharmaceutical corporations), the RCT became a market tool enabling questionable drugs like interferon (IFN) to penetrate the marketplace in the 1980s.⁴⁰ Whistle-blowing books on the pharmaceutical industry point out that it is neither a model of free enterprise nor one of innovation. Moreover, what industry-sponsored research yields is often subject to bias due to conduct and reporting methods.⁴¹

Currently, the RCT acts as a lightning rod in debates about whether EBM is a gift horse or a Trojan horse in health care.⁴² Anthropologists and ethnographers argue its spectre of positivism adumbrates other forms of purportedly valid evidence and ignores patient perspectives. Others see EBM as a managerial tool reinforcing the NHS's bureaucratic top-down approach to regulating the entire health service through 'quality assurance' systems that lead to inappropriate cost-cutting and loss of clinical autonomy.⁴³ Does EBM lead to surveillance medicine, or is it a revolutionary phase in medical progress providing increased transparency of professional knowledge and expertise? The debates rumble on.

Historical perspectives show that the clinical trial did not spring *ex machina* out of Zeus's head but evolved in response to a host of socio-economic factors that shaped the medical profession and its overriding concerns—not least being 'to prove that all treatment must be effective'. In the current climate of contestable evidence about what constitutes effective therapy, the controlled clinical trial is but an epiphenomenon of a deeper underlying unease about the art and science of medicine and the ever increasing gap between the natural and the 'techne'.

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Ethics and experimentation

The disempowered patient: ethics and choice

Jettisoning natural histories of disease (based on external symptoms that made sense to the patient) and delving into the unexplored interior of the body, the so-called ‘clinical gaze’, severed the links with the past and the doctor–patient relationship. The hospital became the scene of death and of the disempowered charity patient in Eugène Sue’s *Les mystères de Paris* (1844):

‘If Dr Griffon wanted to test the comparative effect of a new and quite dangerous medication in order to be able to ascertain its favourable impact on one organ or another, he would take a certain number of patients, treat one group by the new method, another by the old, and leave others solely to the forces of nature... He went on without pity making his patients swallow iodine, strychnine or arsenic to the extreme limits of physiological tolerance or, to put it plainly, to the extinction of life.’

More carefully construed ethical scenarios appeared when the transformation of modern medicine in the late nineteenth and early twentieth centuries (by bacteriology, new technologies and surgical procedures, pharmaceuticals, and the reorganization of the hospital) became increasingly associated with clinical research and human experimentation.

GB Shaw’s drama *The doctor’s dilemma* (1906) considered the rationing of scarce resources—in this case, a vaccine against TB—and raised the question ‘What is the value of different human lives?’. In Lewis’s *Arrowsmith* (1925), the scientific ideals of the medical researcher vs the needs of the experimental population posed the central dilemma. Ordered to the plague-infested West Indies to conduct a controlled trial of his newly discovered ‘phage’ serum, the defining moment came when, succumbing to humanitarian concerns, Martin Arrowsmith gave the serum to all those affected, leaving no control arm.

Nuremberg and all that

Old paternalistic notions about ‘doctor knows best’ came under increasing strain during the interwar period. The normative ethical framework finally became otiose under the racial policies of Nazi Germany, when medical researchers committed crimes against humanity. Voluntary and informed consent headed the list of guidelines for research workers enshrined in the Nuremberg Code after World War II. Later amendments, such as the Declaration of Helsinki (1964), clarified the differences between therapeutic and non-therapeutic experiments. But guidelines and self-policing were insufficient to instil ethical conduct among researchers. The ubiquitous ethical committees that now dominate the landscape of modern research arose after abuses uncovered by MH Pappworth in the UK and HK Beecher in the United States of America (USA). They revealed the routine use of mental defectives and prisoners as human guinea pigs in prestigious medical schools and hospitals, and of cancer patients in risky treatments.^{44,45}

Obvious legal loopholes have been tightened over the years to protect vulnerable groups in clinical research. But, in an age of dependence upon pharmaceutical industry-funded research, the problem has not gone away.

John Le Carré's film *The constant gardener* (2001) is a timely tale set in Kenya about a cover-up of the testing of a TB drug that had severe side effects on trial subjects. In fact, drug disasters have been a major public concern, since thalidomide was withdrawn in 1961 due to horrendous fetal defects. Recent research on drug company-funded RCT drug trials has revealed how the concept of 'equipoise' is violated through comparator bias (making inappropriate comparisons with a placebo, or with too little or too high a dose of the comparator drug).⁴⁶ The events that unfolded at London's Northwick Park Hospital (2006–7), in which a disastrous drug trial left six healthy volunteers with multiorgan failure and little compensation, are poignant reminders that, even in the highly regulated climate of Data and Safety Committees and government guidelines, rules can be bent, conflicts of interest can arise, and public trust can be jeopardized, especially when basic issues, such as safety and informed consent, in clinical research remain ethically refractory.⁴⁷

Plus ça change...

Ben Goldacre's recent analysis⁴⁸ goes to show how much large pharmaceutical companies have undermined every stage of the research and publication process. Firstly, they cherry-pick data from trials, choosing an outcome such as blood cholesterol level, for example, when studying a statin, rather than the death rate or myocardial infarction (MI). Secondly, they can construe positive results either by subgroup analysis, analysis at various time points in the trial, or presenting one of several 2° endpoints as the 1° endpoint. Thirdly, if none of these methods yields satisfactory results, they may hide the results from view. This has the effect of skewing meta-analyses in favour of their drugs, as only positive trials see the light of day.

Those trials that are published may have their results talked up in papers written by ghost writers, ensuring that the interpretation of the data generated is positive. They then add a veneer of respectability to these trials by getting prominent academics to put their names to the papers, despite only tangential involvement. Academics acceding to the wishes of large pharmaceutical companies can garner vital funding for their department and financial rewards for themselves, and further their careers through by gaining publications on their curriculum vitae and being paid to give important talks on the trial. Those who do not agree to put their name to such papers can lose their job.

These factors have resulted in the interests of researchers and institutions, who should be impartial, being skewed towards those of the drug company. The RCT is supposed to be the instrument with which the medical community can dissect out the truth of which treatments are the most effective and in what population. This role has been undermined by the interests of executives and shareholders trumping those of patients—a short-sighted arrangement, as the former are destined to become the latter.⁴⁹

Ways in which to conduct fairer trials have been suggested by people as varied as health-care professionals, such as Ben Goldacre, and the Prime Minister.⁵⁰ Scandinavian countries have so far led the way in using their health-care systems to garner new information, and, in the UK, the data

kept by the NHS (the largest health-care system in the world) could be used to conduct very large-scale RCTs.

As comprehensive patient information is already kept in general practice (GP)'s computer records, the data already exist and could be gathered with little extra effort. The main conundrum would be the randomization process. Ben Goldacre provides a first-hand account of how this complicates the otherwise effortless trials, with rigid consenting procedures making it impractical to carry out in the usual patient–doctor interaction.

Other ways of correcting industry bias have ranged from imposing trial registration databases to funding trials independently of big pharma, something to which the Obama administration pledged \$1 billion. These have promise but have not yet yielded results, either due to imperfect imposition or due to the time and money required to make them work.

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Chronology

Below is a chronological summary of references discussed in this chapter:

Pre-1700s

bc Daniel. *Ch1:1–16*: comparison of diets.

c.900 al-Razi. *The comprehensive book of medicine*: comparison of bloodletting with no treatment group.

1364 Petrarch F. *Letter to Bocaccio, Rerum Senilium V.3*: comparing like with like.

1575 Paré A. *Les oeuvres de M. Ambroise Paré, conseiller et premier chirurgien du Roy*: within-group comparison of wound salve.

1662 Van Helmont JB. *Oriatrike or physics refined*: use of lots in making comparisons.

1700s

1724 Nettleton T. *Part of a letter from Dr. Nettleton, physician at Halifax, to Dr. Jurin*: arithmetic analysis of smallpox inoculation.

1726 Swift J. *Gulliver's travels*: satire on morals and the new mechanical philosophy.

1740 Cheselden W. *The anatomy of the human body*: importance of age-specific outcomes.

1753 Lind J. *A treatise of the scurvy*: first prospective controlled trial of citrus fruit against scurvy.

1764 Stone E. *An account of the success of the bark of the willow in the cure of agues*: dramatic effects in sufficient number of case studies.

1772 Cullen W. *Clinical lectures*: first medical context of 'placebo' to please.

1780 Academy of Medicine, Paris: trials on Mesmer's animal magnetism using blind assessment.

1800s

1834 Trousseau A, Gouraud H. *Répertoire clinique: expériences homéopathiques tentées à l'Hôtel Dieu de Paris. J des Connaissances Médico-Chirurgicales*: first use of inert placebo, bread pill in homeopathy trials.

1835 Louis P. *Recherches sur les effets de la saignée...—la méthode numérique*: founder of modern epidemiology, emphasizing group comparison and population-thinking.

1840 Gavarret J. *Principes généraux de statistique médicale ou développement des règles qui doivent présider à son emploi*: first use of CIs.

1846 Forbes J. *Homeopathy, allopathy and 'young physic'*: use of concurrent arm and blind assessment.

1854 Balfour T, quoted in West C. *Lectures on the diseases of infancy and childhood*: trial of belladonna against scarlet fever—importance of sample size.

1860 Semmelweis I. *Etiology, concept and prophylaxis of childbed fever*: accidentally controlled trial—unacknowledged pioneers of antisepsis.

1865 Sutton H. *Cases of rheumatic fever treated for the most part by mint water*: therapeutic nihilistic use of active placebos.

1900–45

1904 Pearson K. *Report on certain enteric fever inoculation statistics*: first meta-analysis of typhoid vaccination.

1918 Bingel A. *Über Behandlung der Diphtherie mit gewöhnlichem Pferdeserum*: first large-scale, double-blinded trial using alternation.

1923 Fisher R: discovery of notion of randomization.

1931 Doull J, Hardy M, Clark J et al. *The effect of irradiation with ultra-violet light on the frequency of attacks of upper respiratory disease (common colds)*: adoption of random sampling machine to create treatment and control groups.

1934 Greenwood M. *Epidemics and crowd diseases*. Medical Research Council Therapeutic Trials Committee. *The serum treatment of lobar pneumonia*: AB Hill's critique of trial design, especially of alternation and small numbers.

1935 Fisher R. *The design of experiments*: influential text of experimental design using randomization.

1937 Gold H, Kwit N, Otto H. *The xanthines (theobromine and aminophyllin) in the treatment of cardiac pain*: first recognition of countering 'suggestion' in a controlled trial in Anglo-North America.

1945–2000

1948 MRC. *Streptomycin treatment of pulmonary tuberculosis*: first RCT designed by AB Hill.

1948 Nuremberg Code: voluntary consent plus nine other principles governing human experimentation.

1964 *Declaration of Helsinki*: clarification between therapeutic and non-therapeutic experimentation.

1966 Beecher HK. *Ethics and clinical research*: whistle-blowing unethical human experimentation in the USA.

1967 Pappworth MH. *Human guinea pigs*: whistle-blowing in the UK about abuses in routine clinical research.

1972 Cochrane AL. *Effectiveness and efficiency: random reflections on health services*: clarion call for the RCT in health research—'all treatments must be proved effective'.

1995 Moore T. *Deadly medicine: why tens of thousands of patients died in America's worst drug disaster*: RCTs implicated in 1980s antiarrhythmic drug disaster.

1998 Pieters T. *Marketing medicines through randomised controlled trials: the case of interferon*: rise of Big Pharma—the RCT as a marketing tool.

2000s

2000 Djulbegovic B, Lacey M, Cantor A et al. *The uncertainty principle and industry-sponsored research*: 'Big Pharma' and comparator bias in RCTs.

2008 *The creation of the prozac myth*, *The Guardian*: publication bias.

An introduction to evidence-based medicine

How did evidence-based medicine develop? 34

What is the process of evidence-based medicine? 36

How do you assess the quality of a randomized
controlled trial? 42

Statistical terms 46

Can you apply this evidence about a treatment in caring
for your patient? 50

How did evidence-based medicine develop?

Throughout the history of the practice of medicine, clinicians have used 'evidence' from their own clinical experiences, such as the clinical findings from individual patients, to inform decisions about health care. However, with the emergence of new technologies, treatment modalities, and epidemiological methods in the latter half of the twentieth century, some began to question whether we might be doing more harm than good in our attempts to 'cure' disease.

Alvan Feinstein is thought by many to be the founding father of clinical epidemiology, the science underpinning EBM. His seminal book urged clinicians to be more scientific about the practice of clinical medicine and was published two decades after the end of World War II, during an era of new large-scale epidemiologic studies such as the Framingham Heart Study (1949), the Salk vaccine trial (1954), and the Surgeon General's report on 'Smoking and health' (1964).

In 1971, Archie Cochrane also wrote an important and controversial book, suggesting that clinicians were perhaps overly devoted to their patients, with many overtreating in an effort to do everything possible to 'cure'. He argued that the systematic application of medical research, in particular evidence from RCTs, should be encouraged, so as to maximize the use of therapies proven to be safe and effective and to minimize the impact of ineffective and unsafe ones.

David Sackett and colleagues developed these concepts further when they wrote about clinical epidemiology and the 'science of the art of medicine'. Their book described ways in which the principles of population epidemiology might be applied to individual patients' care decisions and, in particular, the appraisal of research for quality.

As this book will highlight, there are many 'key' clinical trials that have had a profound impact on the effective practice of medicine in the manner that Feinstein, Cochrane, and Sackett proposed. In the wider medical literature, one will unfortunately find many examples of poorly conducted trials, which could do harm if their results were applied to clinical practice. There are also examples of simple and effective treatments that have not been adopted into practice and perhaps should be. This book, as we have explained, is not a comprehensive summary of evidence-based clinical practice; it simply highlights some of the many key clinical trials of effective treatments that are relevant to clinical practice today.

What is the process of evidence-based medicine?

'The practice of evidence-based medicine means integrating clinical expertise (proficiency, judgement acquired through clinical practice and use of individual patient's right, predicaments, preferences) with the best available expert evidence from systematic research.'

This definition, from Sackett's seminal paper in 1996, has been translated into five steps, which we shall refer to in this chapter as the 'Five As'. These were designed to help clinicians find the best available expert evidence from a systematic search. Most clinicians would practise at least the first four of these steps, as outlined in this section.

The development of the EBM process has been an important step towards helping clinicians keep up-to-date at a time where clinical medicine is advancing rapidly and patients are becoming more involved in health-care decisions. It is impossible for a single clinician to be familiar with all of the best evidence they might need for their daily clinical practice. An analysis of 100 of the best-quality systematic reviews published in the journal *ACP Journal Club* between 1995 and 2005 showed that the median survival time before new and important evidence was found on a particular topic was 5 years. Almost 25% were out of date within 2 years, and a further 7% before the article had even been published.

Books like this, which summarize some of the highest-quality evidence, may simplify part of the process for busy clinicians; however, they alone will not always be able to answer the question that faces a clinician or their patient. Therefore, the following five steps provide a framework for clinicians who wish to incorporate the best scientific evidence into their clinical decisions.

STEP 1—Asking

Some would argue this to be the most important step in the EBM process. Before rushing onto the Internet to search for an answer, it is important to pause and think about what your precise question is. There are two aspects to this:

A. Refining your question

Refining a question into several parts using the PICO (Population/Patient problem, Intervention, Comparison, Outcome) framework can help identify useful keywords for a search and will increase the chances of finding an appropriate answer to the question. Most of us have experienced the frustration of typing ill-defined keywords into a general search engine such as Google and ending up with countless irrelevant 'hits'. Therefore, using a framework, such as PICO, to develop the best keywords can save a considerable amount of time. The components of the PICO framework are shown in Box 2.1.

Box 2.1 The PICO framework for refining a clinical question

i. Population/Patient problem

Describe who the question pertains to (e.g. elderly men with prostate cancer or toddlers with otitis media).

ii. Intervention

Define what treatment, test, or exposure is being considered in this case (e.g. oral penicillin, back exercises, smoking exposure). It is also useful to define some of the details (e.g. duration, dose), i.e. the 'when' and 'where'.

iii. Comparison

Define against what the intervention would be compared (e.g. oral vs topical therapy, proposed intervention vs placebo/gold-standard intervention or criteria). Note that this section may not always be relevant.

iv. Outcome

Define the outcomes that are important and relevant for the patient (e.g. pain relief, return to work). We often focus exclusively on the beneficial outcomes of treatment, but we should also consider the importance of minimizing the associated risks or harm (e.g. side effects, long-term complications).

B. Defining the question type

The second part of 'asking' is to define the *type* of question that is being asked. A number of researchers have systematically analysed the types of questions that clinicians ask. The most frequent questions pertain to treatment, with questions about the cause or 'aetiology' of a condition and 'diagnosis' questions also being common.

It is important to consider the type of question, so that the best source of evidence can be used to find the answer. To illustrate this first step of the EBM process, let us consider a hypothetical case:

Daniel, a 2-year-old ♂, comes to see you with a 3-day history of fever, irritability, and runny nose. On examination, he has a temperature of 38°C and an erythematous, dull right tympanic membrane. The rest of the physical examination is normal. His mother says they are about to go on holiday, and she wants him to get better as quickly as possible.

The unstructured or 'raw' question that our hypothetical practitioner first asks is:

'Should this patient be prescribed an antibiotic?'

The *Population/Patient problem* in this case would be 'child with acute otitis media'; the *Intervention* is 'antibiotics'; the *Comparator* is 'watch and wait', and the *Outcomes* are 'symptom relief'. This is a question about treatment.

Having ‘asked’ an answerable question, the next step in the process of EBM is to ‘access’ the evidence to search for an answer.

STEP 2—Accessing


It is impossible to cover this issue comprehensively in this introductory chapter. With an ever increasing number of evidence-based resources, accessibility and costs need to be considered; some resources are only available for a subscription fee, to which not all institutions will subscribe. This section will focus on the generic principles of searching that should be applicable in a wide range of contexts, at minimal or no cost.

A. *Selecting and combining keywords for the search strategy*

Generally speaking, the PICO framework can be used as the basis of a search strategy, with, in the first instance, a combined *Patient/Problem AND Intervention*. If this remains too broad, then one or more of the Outcomes can always be added. Referring back to our case example about Daniel, we might consider ‘otitis media’ AND ‘child’ AND ‘antibiotic’. If that yields more results than are manageable, then ‘otitis media’ AND ‘antibiotic’ AND ‘symptom relief’ may be tried to further refine the results. For a more comprehensive searching, ‘medical subject headings’ (MeSH), alongside more detailed searching strategies, should be applied.

B. *Matching the question type against the best study design, taking into account the quality of evidence*

Research involves measurement of various outcomes, including the effects of treatment and the accuracy of tests. All measurements have some random error, attributable to chance. However, measurements can also be subject to systematic error or bias. The best evidence avoids these pitfalls. This book deliberately focuses on well-conducted RCTs, wherever possible, because they are the best type of study to answer questions about treatment.

Table 2.1 on  p. 39 shows study designs that answer treatment questions. The further down the list (or levels of evidence), the greater the risk of bias. Randomizing participants in a study reduces bias, because confounding factors (such as age, gender, smoking status, etc.) are evenly distributed between the intervention and control arms of the study. In other words, the only difference between the groups is whether or not they receive the intervention, since their allocation to a particular arm of the study is purely by chance. Expert opinion or clinical experience is more open to bias. However, in some cases, particularly for rare events and conditions, this might be the only evidence available.

The list in Table 2.2 summarizes the most recent ‘quality of evidence’ framework developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group. Although this framework was developed mainly to help guideline developers make evidence-based recommendations, its approach to assessing the quality of evidence is widely used and makes the important distinction between evidence quality and the strength of a recommendation. It also helps to point out the importance of looking at the ‘body of evidence’ for a clinical question.

Table 2.1 Levels of evidence

| Level | Type of evidence |
|-------|---|
| 1a | Evidence from systematic reviews or meta-analysis of RCTs |
| 1b | Evidence from at least one RCT |
| 2a | Evidence from at least one controlled study without randomization |
| 2b | Evidence from at least one other type of quasi-experimental study |
| 3 | Evidence from non-experimental descriptive studies such as comparative studies, correlation studies, and case control studies |
| 4 | Evidence from expert committee reports or opinions and/or clinical experience of respected authorities |

Table 2.2 A summary of GRADE's approach to rating quality of evidence

| Study design | Initial quality of body of evidence | Lower if | Higher if | Quality of body of evidence |
|-----------------------|-------------------------------------|--|---|---------------------------------|
| Randomized trials | High \Rightarrow | Risk of bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious | Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding | High++++ Moderate +++ |
| Observational studies | Low \Rightarrow | Imprecision -1 Serious -2 Very serious Publication bias -1 Serious -2 Very serious | +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed | Low ++ Very low + |

Adapted from Balshem H, Helfand M, Schunemann HJ, et al. (2011) GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epi* 64, 401–6.

While it is important to consider using RCT evidence, if at all possible, it is not always feasible to randomize people in a study. The reasons for this may be both practical and ethical. This will be the case particularly for studies that look at prognosis or aetiology. It is clearly impossible to randomize someone to 'get breast cancer' or to 'not get breast cancer'. However, it is possible to follow up women who have breast cancer and compare them with a similar group of women who do not have breast cancer, and to then look for associated factors.

C. Identifying the best source for accessing this study type

Studies published in peer-reviewed journals can usually be accessed through electronic databases, usually based around particular content areas. Journals and their articles may be contained within more than one database if they are applicable to more than one content area. *Medline* is the most commonly encountered database of medical journals. Other examples include *Cinahl* (includes many nursing and allied health journals) and *PsychInfo* (contains many psychology journals).

Medline: Medline is the US National Library of Medicine (NLM)'s premier bibliographic database. It contains about 19 million references to journal articles in life sciences, with a concentration in biomedicine dating back to 1966. A technical committee selects which journals are included, and participating journals submit their citations every time a new issue is published. Since 2005, 2,000–4,000 citations have been added each day from Tuesday to Saturday, with nearly 700,000 added in 2010. More information about the NLM can be found at ☞ <http://www.nlm.nih.gov>.

Searching the electronic databases can be done via a search engine. A single search engine might be able to access several indexes, websites, or databases. Equally, a single database might be accessible via several search engines. For example, *Medline* can be searched using *Entrez PubMed* (☞ <http://www.ncbi.nlm.nih.gov/sites/entrez>), *Ovid Silver Platter* software, or even *Google Scholar* (☞ <http://scholar.google.com>).


Although some search engines and databases are available free of charge, others require a subscription and limit free access to the abstract only. Therefore, your ability to access some evidence will be restricted by your local employer's or library's subscriptions. This can be a problem for those in remote settings or low-income countries, or for self-employed practitioners. In the UK, an *Athens* login is sometimes required to procure access to certain resources (☞ <http://www.openathens.net/>). Universal free access to *Medline* via *PubMed* provides free access to all abstracts, as well as to some full-text versions of journals. It can be accessed by either typing 'PubMed' into any web search engine or by using the links above.

Applying these principles to our case study example gives the following result:

Typing 'antibiotics AND 'otitis media' AND 'children' into PubMed provides over 3,000 journal articles, which cover a whole range of study types.

In routine practice, 3,000 hits is an impractical number to review. Therefore, some search engines, such as *Ovid* and *Entrez PubMed*, have pre-programmed 'filters' that can be applied to limit the search to particular study types. In this example, it would be useful to limit the search to systematic reviews of RCTs, since these will provide the highest level of evidence for answering a treatment question.

The Cochrane Library: We now find a *Cochrane* review on 'Antibiotics for acute otitis media in children' (containing a summary of the results of 12 RCTs on this topic) at the top of the results. The Cochrane Library's

database of systematic reviews is perhaps one of the most useful resources for therapy-related questions. It is available through  <http://www.cochranelibrary.com>. Abstracts are free.

Limiting the search to systematic reviews using the filter called 'systematic reviews' on PubMed, or 'Limits' on Ovid, provides 164 'hits'.

STEP 3—Appraising critically







This step involves assessing the quality of a study. A poorly conducted systematic review or RCT may not be worth considering, as the results may be misleading due to methodological flaws and sources of bias. Numerous checklists have been developed to help clinicians decide whether a study is valid or not. On  pp. 42–4 in this chapter, we will look at the appraisal process for RCTs in much greater detail, as this study type is the focus of this book. Table 2.3 summarizes a number of widely used checklists for appraising and reporting on a broader range of study types that will not be covered in further detail here but may be useful for readers in other contexts.

Table 2.3 Common appraisal and reporting checklists

| Checklist source | Study types | Location |
|--------------------------|--------------------------------------|---|
| JAMA Users' Guide Series | All |  www.jamaevidence.com |
| PRISMA | Systematic reviews |  www.prisma-statement.org/ |
| GRADE | Clinical practice guidelines |  www.gradeworkinggroup.org/ |
| CONSORT | RCTs |  www.consort-statement.org |
| STROBE | Non-randomized observational studies |  www.strobe-statement.org/ |


STEP 4—Applying

This step remains one of the most challenging, yet most important, steps within the EBM process. One may argue that this embodies the true art of medicine, as it requires the 'integration of best evidence with clinical expertise, the patient's circumstances, and their personal preferences.' A recent study of general practitioners (GPs) found that being able to tailor evidence appropriately to individual patient decisions remained a major barrier to the use of evidence in practice. By contrast, access to the Internet and attitudes towards EBM had improved. Most practitioners in this study also expressed a preference for involving their patients in making decisions, yet useful tools to facilitate this remained largely underutilized. We will explore this in greater detail later in the chapter.

STEP 5—Assessing

This is not always practiced by clinicians but is a potentially useful step that requires the clinician to reflect upon the previous four steps and consider ways in which they might be improved in subsequent efforts.

How do you assess the quality of a randomized controlled trial?

Given the focus of this book, this section will discuss the appraisal of RCTs only. As mentioned in the previous section, there are many well-developed and frequently used checklists for appraising the quality of a study. Here, we will focus on the JAMA (*Journal of the American Medical Association*) checklist (Box 2.2). As you develop your EBM skills, you may find that a different checklist suits your needs. While not developed specifically for critical appraisal, the CONSORT checklist was developed in the early 1990s by a group of journal editors, trialists, and methodologists who wanted to improve the quality of reporting on clinical trials. The outcome was the CONSORT statement (*CONsolidated Standards Of Reporting Trials*), a useful point of reference (see website link on  p. 41).

Box 2.2 The JAMA quality assessment checklist for RCTs

*I. Are the results of this single preventive or therapeutic trial valid?**

Main questions to answer:

1. Was the assignment of patients to treatments randomized? Was the randomization list concealed?
2. Were all patients who entered the trial accounted for at its conclusion? Were they analysed in the groups to which they were randomized?

Finer points to address:

3. Were patients and clinicians kept 'blind' to which treatment was being received?
4. Aside from the experimental treatment, were the groups treated equally?
5. Were the groups similar at the start of the trial?

II. Are the valid results of this study important?

III. Can you apply this valid, important evidence about a treatment in caring for your patient?

1. Do these results apply to your patients?
 - a. Is your patient so different from those in the trial that its results cannot help you?
 - b. How great would the potential benefit of therapy actually be for your individual patient?
2. Are your patient's values and preferences satisfied by the regimen and its consequences?
 - a. Do you and your patient have a clear assessment of their values and preferences?
 - b. Are these met by this regimen and its consequences?

* Adapted From Sackett, Richardson, Rosenberg and Haynes (1997) *Evidence-Based Medicine: How to Practice and Teach EBM*. Churchill Livingstone, London.

Methodology: will the randomized controlled trial design produce valid results?

Null hypothesis and errors: The null hypothesis is a hypothesis formed at the outset of a study involving a treatment vs control, which is presumed true, unless nullified or refuted by statistical evidence. For example, when comparing a drug with placebo, the null hypothesis would be 'the new drug is of equal efficacy to the placebo'. Statistically significant analysis of the data would then be required, in order to prove that the new drug was more effective. Two types of errors can subsequently arise:

- Type 1 or α : rejecting a hypothesis that should have been accepted (false positive), i.e. stating that a difference was observed when this was not actually the case.
- Type 2 or β : accepting a hypothesis that should have been rejected (false negative), i.e. stating that no difference was observed when, in fact, a difference was present.

Bias: Bias, the systematic over- or underestimation of the true effect, can be introduced at a number of stages. The main sources of bias in RCTs come from either poor randomization and/or through loss to follow-up after randomization.

Randomization: The method of randomization is very important in a trial. Where possible, it should be done independently, so that the researchers are 'blinded' to the allocation of participants. Randomly allocating participants to treatment or control groups is a highly effective way of reducing bias, as it ensures both groups are likely to be very similar (i.e. similar baseline characteristics) to begin with. Any differences between the two groups are then most likely to be attributable to the intervention itself.

Blinding: Blinding participants (and/or researchers), when measuring the outcomes of interest, is a method by which studies can attempt to reduce the unwanted influences of bias and improve internal validity. This can take several forms: *single-blind* (patient is unaware which intervention they have been allocated), *double-blind* (both researcher (clinician) and patient are unaware to which intervention the patient has been allocated); *triple-blind* (when the researcher, patient, and outcome assessor do not know to which intervention the patient has been allocated). There are a number of types of bias, some of which can be found in Fig. 2.1.

Follow-up: Another important factor to check is whether or not patients have been adequately followed up. In particular, this should be to ensure that there has not been a high dropout rate in one arm of the trial, compared with the other. Participants should not be swapped from one group to the other. If this does unavoidably occur for ethical or other reasons, then the analysis should consider what would have happened had they stayed in their original group (sometimes called 'intention-to-treat' analysis). Omitting the patients who withdrew may overestimate treatment effects.

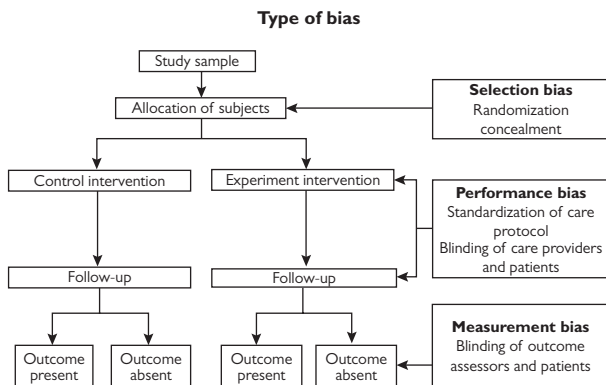


Fig. 2.1 Types of bias. Reproduced from: Khan K, Kunz R, Kleijnen J, Antes G. (2003) Systematic reviews to support evidence-based medicine: How to review and apply findings of systematic reviews. *BJS*, 91:3 p375, Royal Society of Medicine Press, London, with permission from John Wiley and Sons.

Are the valid results of this study important?

There are a range of statistical tools available to quantitatively assess the relative importance and significance of study data. It is crucial to select the appropriate test for the particular data in a study. Although there is no single algorithm that can be applied to determine which test is best in every case, a decision tree can help. Further discussion of this is well beyond the scope of this book, but there are a number of helpful Internet-based resources such as:

- *Handbook of Biological Statistics*: <http://www.biostathandbook.com/testchoice.html>.

Statistical terms

The size and direction of the effect of a treatment (i.e. dichotomous data) is often reported as an ‘odds ratio’ (OR), ‘relative risk’ (RR), ‘hazard ratio’ (HR), or the ‘difference in means’. To see if there is much error around this estimate, the ‘95% confidence interval’ can be calculated to ensure that it does not cross the null value (the point of no effect). Whether or not there is a statistically significant effect can be determined by seeing whether the ‘p-value’ is <0.05. We will now examine some of the key terminology in more detail.

A. Difference between group means

Used for continuous data, e.g. the mean reading score in treatment group A minus the mean reading score in the control group B.

B. Relative risk (RR)

This is the risk of outcome in the treatment group relative to the other (usually control) group. It is a ratio. For example, using values for our antibiotics and otitis media example, the proportion of children who took antibiotics and still had ear pain after 4–7 days (19%) is divided by the proportion of children in the control group with ear pain persisting at 4–7 days (25%) to give an RR = 0.76. An RR = 1.0 means that there is no effect of the treatment. In other words, this implies that there was no difference between treatment and control groups (i.e. the null value). If the RR is >1.0 for an adverse outcome, such as death, this generally means the effect is harmful. If the RR is <1.0, then the treatment is protective. To use our example, an RR = 0.76 means that children in the treatment group are 24% less likely to have ear pain at 4–7 days, compared with controls. The further away the RR is from the null value, the greater is the effect of the treatment.

Outcome and exposure status

See Table 2.4.

Table 2.4 Outcome and exposure table

| | Outcome present | Outcome not present | |
|---|-----------------------------|--------------------------------|----------------------------|
| Exposed to treatment: treatment group | A | B | Number exposed (A + B) |
| Not exposed to treatment: control group | C | D | Number not exposed (C + D) |
| | Number with outcome (A + C) | Number without outcome (B + D) | |

$$\begin{aligned} \text{RR} &= \frac{\text{proportion with outcome in treatment group}}{\text{proportion with outcome in control group}} \\ &= \frac{A/(A+B)}{C/(C+D)} \\ &= \frac{\text{exposure event rate (EER)}}{\text{control event rate (CER)}} \end{aligned}$$

C. Relative risk reduction (RRR)

Rather than trying to discuss the effect of a treatment as a ratio, it is often more clinically relevant to express the effect as a difference. This can be done in relative (i.e. in relation to the effect on controls) or absolute terms (which shows the actual size of the effect on that particular population—see the next section). The RRR will be the same, regardless of the population. It can be calculated, using the following formula:

$$** \text{ RRR} = \frac{(\text{CER} - \text{EER})}{\text{CER}}$$

If we consider this for our example, the RRR would be $(25\% - 19\%) / 25\% = \text{a } 24\%$ reduction in ear pain at days 4–7.

D. Absolute risk reduction (ARR)

In contrast to the RRR, the absolute risk reduction (ARR) is simply the difference between the event/outcome rate in the treatment group and that of the control group:

$$** \text{ ARR} = \text{CER} - \text{EER}$$

The ARR is said to be a much more clinically relevant estimate of the effect, because it takes into account the prevalence of an outcome in that particular population. In our otitis media example, the symptom rate at days 4–7 in the control population is 25%. This may be because the research has been conducted in a population with average rates of bacterial infection. The ARR for this study would be $(25\% - 19\%)$, which is a 6% reduction in sore throat by using antibiotics. However, if the study were conducted in a higher-risk population where the prevalence of bacterial infection in the control group was 50%, then the ARR would be much greater. You may recall that, in this example, the RR was 0.76, so we would expect the treatment group in this higher-risk population to have a symptom rate of around 38%. In other words, the ARR for this higher-risk population is $(50\% - 38\%)$, which is 12% (compared to 6% in the average-risk population).

Hopefully, you can now see how important it is to consider whether you are using a *relative* or an *absolute* risk reduction. The ARR in this example shows that using antibiotics in the high-risk population will prevent many more cases than in the average-risk population. This is a point that might be very relevant when considering the trade-off between the benefits and harms or the costs of treatment.

E. Number needed to treat (NNT)

This is the number of patients who need to be treated with the studied intervention, in order to prevent one event. It is calculated as the inverse of the ARR:

$$\text{NNT} = \frac{1}{\text{ARR}}$$

In our hypothetical otitis media example, we would find that the NNT for the ‘high-risk’ population would be $1/0.12$ or 8.33. This means that we would need to treat just over eight patients to prevent persistent ear pain. In the ‘low average-risk population’, the NNT would be $1/0.06$ which is 16.7. In other words, in the average-risk population, we need to treat

17 children with antibiotics to prevent one persistently painful ear, but only 1/0.12 or eight children in the higher-risk group.

It is important to note that the NNT is only applicable when the study population is similar to the target patient population for whom the tested intervention is intended. When the treatment increases the risk of the harmful outcome, then the inverse of the risk difference is called the 'number needed to harm' (NNH).

F. Odds ratio (OR)

We often talk about the 'odds' of an event occurring. The 'odds'—or chance—of us winning the lottery is small. This seems obvious, but how do we measure the odds of a clinical event occurring? The OR is the ratio of the odds of a disease occurring in the presence of an exposure relative to the odds of the disease occurring in the absence of the exposure. The OR is commonly used in case control studies.

Looking back to the 'outcome and exposure status' table, the OR can be defined by the following formula:

$$\begin{aligned}\text{OR} &= \frac{\text{odds of disease in the presence of exposure}}{\text{odds of disease in the absence of exposure}} \\ &= A/B \text{ divided by } C/D \\ &= AD/BC\end{aligned}$$

Therefore, this is the odds of the outcome in the treatment group relative to the odds of the outcome in controls. Again, an OR of 1.0 means that there is no difference between the treatment and control groups. An OR >1.0 for an adverse outcome, such as death, means an increased risk. In some studies, the OR is a reasonable estimate of the RR, but only if the outcome is uncommon.

G. Hazard ratio (HR)

Used in survival analysis, this is the probability of a hazard at time 't' in the treatment group, compared with the probability of a hazard at time 't' in the control group, i.e. the effect of a variable upon the risk of an event. Sometimes, the HR is simply referred to as the 'relative risk'.

H. 95% confidence interval (CI)

The terms outlined in this section (RR, OR, HR, and difference of the means) are all estimates of the effect of the study factor on the population in question. However, there will always be some error associated with this, particularly if there are only a small number of people participating in the study (i.e. a small sample size). The 95% CI is the range within which we are 95% confident that the true estimate of the effect lies. Note that, if the 95% CI for an OR or RR value crosses 1.0 (the point of no effect), then it is possible that the true effect is none, i.e. the effect is not statistically significant.

I. p-values and statistical significance

A p-value is the probability of the observed difference being due to chance. Traditionally, if the p-value is <0.05, then the result is considered statistically significant.

J. Tools applicable to diagnostic studies

These studies investigate the ability of a particular diagnostic or screening test to detect a disorder in the sample population (Table 2.5). The performance of the test can then be evaluated:

- Sensitivity: proportion of people with a disorder that are correctly diagnosed as positive by the test. The higher the sensitivity of a test, the more likely a negative result will rule out the presence of the disorder (high *SeNsitivity* rules *OUT* = SNOOUT).
- Specificity: proportion of people without the disorder that are correctly excluded as negative by the test. The higher the specificity of a test, the more likely a positive result will rule in the presence of the disorder (high *SPecificity* rules *IN* = SPIN).
- Positive predictive value (PPV): proportion of people with a positive test who actually have the disorder.
- Negative predictive value (NPV): proportion of people with a negative test who do not have the disorder.
- Likelihood ratio (LR): provides a direct estimate of how much a test result will change the odds of having a disease. The LR for a positive result (LR+) is how much the odds of the disease increase when a test is positive. The LR for a negative result (LR-) is how much the odds of the disease decrease when a test is negative.

Table 2.5 Sensitivity and specificity

| | Disorder present | Disorder absent |
|---------------|------------------|-----------------|
| Positive test | a | b |
| Negative test | c | d |

$$\text{Sensitivity} = a / (a + c)$$

$$\text{PPV} = a / (a + b)$$

$$\text{Specificity} = d / (b + d)$$

$$\text{NPV} = d / (c + d)$$

LR = probability of test result in someone with the disease / probability of test result in someone without the disease

$$\text{LR+ (+ve test)} = \text{sensitivity} / (1 - \text{specificity})$$

$$\text{LR- (-ve test)} = (1 - \text{sensitivity}) / \text{specificity}$$

Can you apply this evidence about a treatment in caring for your patient?

Several issues need to be considered when generalizing the results of an RCT for a particular patient population. This is often a sticking point for practitioners who frequently find themselves trying to apply either hospital-based studies or studies conducted in other countries with different health-care systems and patterns of disease to their own community-based populations. Trials conducted in hospital clinics may include higher proportions of patients with more serious disease than community-based samples, a factor that needs to be considered. The following questions on should be considered:

What is the role of the patient in applying evidence?

Sackett's definition of EBM, quoted at the beginning of this chapter, clearly includes patient preference as an important component. However, to what extent do patients want to be involved in health-care decisions? A survey of over 8,000 people in eight European countries showed that the majority of people do want some active role. The extent to which patients want to be involved may vary with culture, age, and socio-economic group, as well as with the disease and its severity.

However, a direct link between patient involvement in decision-making and improved health and well-being is poorly documented. McNutt succinctly argues that patient involvement in decision-making is concerned with two things: (1) informing them of the consequences of the available options, including the probabilities of these where available, and (2) the opportunity to trade off the benefits and risks for them. This may not result in the patient actually making the final decision but does describe a process of involvement.

There has been increasing interest in 'decision aids' as effective tools for increasing patient involvement in decision-making. A *Cochrane* review of 86 RCTs concluded that decision aids increased patient knowledge of the options, compared to usual care, had a positive effect on doctor-patient communication, increased patient involvement, reduced decisional conflict, and, for those with explicit values, clarification exercises increased informed values-based choices. Decision aids also increased realistic expectations of the benefits and harms of different options (as measured by patients' perception of the probability of outcomes).

In our example of 2-year-old Daniel with acute otitis media, the mother's preference for reducing the chance of persistent pain due to their upcoming holiday travels may outweigh the risks of antibiotic side effects in her decision.

Beyond this book: what is the role of systematic reviews and clinical practice guidelines?

For some clinical questions, there have been a number of good-quality RCTs conducted across different populations, and these are often summarized in systematic reviews. Clearly, if a good-quality systematic review summarizes and pools the results of several RCTs, then that source of evidence should

be considered. The *Cochrane* database of systematic reviews is an excellent source of such evidence. If results from several trials can be pooled quantitatively (into a meta-analysis), this will provide a summary estimate of the effect of the treatment. Clinical practice guidelines are often a locally derived summary of systematically derived evidence, which has taken into account local application and health system contexts. They may also be an excellent source of evidence. The GRADE group suggest that, when considering a recommendation to apply evidence (or not), there are four domains that need to be considered:

1. Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) (trade-offs).
2. Confidence in the magnitude of estimates of the effect of the interventions on important outcomes (overall quality of evidence for outcomes).
3. Confidence in values and preferences and variability.
4. Resource use.

However, it is important to note that not every clinical condition or topic will necessarily have a simple, accurate, up-to-date, and unbiased research-based answer. As an adjunct to clinical expertise, EBM has become increasingly central to medical practice, providing the impetus for ensuring health-care professionals remain up-to-date with advances.

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Part 2

Medical specialties

Cardiology

- Introduction 56
- Coronary artery disease: statins 58
- Hypertension: optimal treatment 60
- Myocardial infarction: clopidogrel and metoprolol 62
- Myocardial infarction: pre-hospital thrombolysis vs primary percutaneous intervention 64
- Myocardial infarction: thrombus aspiration 66
- Non-ST elevation acute coronary syndrome: fondaparinux 68
- Non-ST elevation acute coronary syndrome: ticagrelor 70
- Non-ST elevation acute coronary syndrome: enoxaparin 72
- Non-ST elevation acute coronary syndrome: clopidogrel 74
- Non-ST elevation acute coronary syndrome: timing of intervention 76
- Coronary artery disease: percutaneous intervention 78
- Coronary artery disease: revascularization vs medical care in diabetes 80
- Coronary artery disease: PCI vs CABG in diabetes 82
- Coronary artery disease: PCI vs CABG in multivessel disease 84
- Heart failure: β -blockers 86
- Heart failure: spironolactone 88
- Heart failure: angiotensin II receptor antagonists 90
- Heart failure: implantable cardioverter–defibrillator vs amiodarone 92
- Heart failure: cardiac resynchronization therapy 94
- Heart failure: revascularization 96
- Atrial fibrillation: rate vs rhythm control 98

Introduction

'After all, in spite of opinion, prejudice or error, Time will fix the real value upon this discovery, and determine whether I have imposed upon myself and others, or contributed to the benefit of science and mankind.' (William Withering, 1785)

So said William Withering in his *Account of the foxglove and some of its medical uses*, in which he described the therapeutic effects of foxglove extract in a series of patients with dropsy. His seminal observations sparked a debate about the benefit of digitalis, the active ingredient of foxglove, which was to continue for over two centuries. Controversy was only finally resolved in 1997 with the publication of a randomized, placebo-controlled trial in over 7,000 patients with heart failure (HF).

To date, several thousand randomized trials of cardiac treatments have been published, and, over the past few decades, clinical cardiology has gradually evolved from an experience-based towards an evidence-based specialty. Cardiologists, once revered for their prowess with a stethoscope, are now as likely to be discussing the results of the latest randomized trial as the nuances of cardiac auscultation. The current generation of cardiologists often refer to themselves as 'plumbers', 'electricians', or 'imagers', depending on their subspecialty interest, but all have access to an extensive and growing therapeutic armamentarium, increasingly supported by the results of randomized clinical trials.

Selecting a small number of trials for a chapter on evidence-based cardiology is therefore challenging. We have attempted to make an eclectic selection and to provide a balanced interpretation of the trial results. All of the trials have influenced cardiological practice, but integration of the evidence from them into routine patient management is not easy. Randomized trials recruit selected patients, and the results may not be applicable to the generality of patients with cardiac disease. Women and the elderly are, for instance, often under-represented. Moreover, analyses of clinical trials often emphasize subgroup analyses, but the pitfalls of this approach were illustrated by the ISIS-2 investigators who reported that patients with acute MI born under the astrological star signs Gemini and Libra seem not to benefit from aspirin!

Astute clinicians will also recognize that there are other valuable sources of evidence, apart from randomized trials; some years ago, proponents of evidence-based practice were invited to volunteer for a randomized clinical trial of parachute use during gravitational challenge—not surprisingly, there were few takers!

We hope this chapter may help to familiarize clinicians with some of the evidence underpinning contemporary cardiological practice and encourage interest in the future development of the cardiological evidence base.

Coronary artery disease: statins

4S (Scandinavian Simvastatin Survival Study): Randomized trial of cholesterol-lowering in 4,444 patients with coronary heart disease.

AUTHORS: Pedersen T, Kjekshus J, Berg K *et al.*

REFERENCE: *Lancet* (1994) **344**, 1383–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with established coronary artery disease (CAD) and total cholesterol levels of 5.5–8.0mmol/L, the addition of simvastatin to regular medical therapy results in a 30% reduction in total mortality, relative to placebo, with no effect on non-cardiac mortality.

Impact

Lipid-lowering therapy with a statin is now part of the standard treatment of patients with coronary heart disease (CHD).

Aims

Epidemiological evidence demonstrates a powerful association between hypercholesterolaemia and CHD, with early studies of cholesterol-lowering for both 1° and 2° prevention demonstrating reduced CHD events. Nevertheless, drug treatment for hypercholesterolaemia remained controversial, as no mortality outcome data were available, and an increase in the risk of non-cardiac death from cancer or violence had been reported. This trial was designed to study the effects of long-term treatment with simvastatin (a 3-hydroxy-3-methylglutaryl coenzyme A [HMGCoA] reductase inhibitor) on mortality and morbidity in patients with CHD.

Methods

Patients: 4,444 patients at 94 Scandinavian centres.

Inclusion criteria: Compliance with 2-wk placebo run-in, and:

- Age 35–70y, with previous MI or angina;
- Fasting cholesterol level 5.5–8.0mmol/L after dietary advice;
- Fasting triglyceride level <2.5mmol/L after dietary advice.

Groups:

- Dietary advice and simvastatin 20mg daily, increased to 40mg daily if total cholesterol exceeded 5.2mmol/L ($n = 2221$);
- Dietary advice and matching placebo ($n = 2223$).

Primary endpoint: Total mortality.

Secondary endpoint: ‘Major coronary events’—coronary deaths, definite or probable hospital-verified non-fatal MI, resuscitated cardiac arrest, definite silent MI verified by electrocardiogram (ECG).

Other endpoints: Myocardial revascularization (coronary artery bypass graft—CABG, or percutaneous coronary intervention—PCI).

Follow-up: Mean follow-up (F/U) = 5.6y.

Results

Treatment with simvastatin was associated with reductions in serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, but a significant increase in high-density lipoprotein (HDL) cholesterol (Table 3.1).

Table 3.1 Summary of results

| | Simvastatin | Placebo | RRR (95% CI) | p |
|--|--------------|-------------|------------------------|--------------|
| Mean change in total cholesterol | 25% decrease | 1% increase | Not reported | Not reported |
| Mean change in LDL | 35% decrease | 1% increase | Not reported | Not reported |
| Mean change in HDL | 8% increase | 1% increase | Not reported | Not reported |
| Mean change in triglycerides | 10% decrease | 7% increase | Not reported | Not reported |
| 1° endpoint: death | 182 (8%) | 256 (12%) | 0.70 (0.58 to 0.85) | 0.0003 |
| 2° endpoint: 'major coronary events' | 431 (19%) | 622 (28%) | 0.66 (0.52 to 0.8) | 0.00001 |
| All coronary deaths | 111 (5%) | 189 (8.5%) | 0.58 (0.46 to 0.73) | Not reported |
| All non-cardiovascular deaths | 46 (2.1%) | 49 (2.2%) | Not reported | ns |
| Coronary surgery or angioplasty | 252 (11.3%) | 383 (17.2%) | 0.63 (0.54 to 0.74) | <0.00001 |
| Fatal and non-fatal cerebrovascular events | 70 (3.2%) | 98 (4.4%) | 0.70 (0.52 to 0.96) | 0.02 |

Discussion

This trial demonstrated for the first time that, in patients with overt CHD, the addition of simvastatin to standard medical therapy significantly reduced mortality and morbidity. The 10-y F/U data are now available for this study, and, although >80% of the two groups were ultimately on open-label statin therapy, the survival benefit of an initial 5-y statin treatment persisted, with no increase in cancer deaths up to a median F/U of 10.4y. Subsequent trials (e.g. LIPID: *N Engl J Med* (1998) 339, 1349–57; CARE: *N Engl J Med* (1996) 335, 1001–9; HPS: *Lancet* (2002) 360, 7–22) have confirmed the beneficial effects of statin therapy. In a meta-analysis of 14 such trials (including >90 000 patients), statin therapy reduced the 5-y incidence of major coronary events, myocardial revascularization, and stroke by about 1/5 per mmol/L reduction in LDL cholesterol. The absolute benefits of statin therapy were largely independent of the initial lipid profile but were determined by the absolute risk of adverse vascular events and the absolute reduction in LDL achieved.

Problems

- Only 19% of patients were women, and the mortality rate for women in the placebo group was half that of men. Nevertheless, simvastatin reduced the risk of major adverse events in women to roughly the same extent as in men, and the benefits of treating women have been confirmed in meta-analyses.

Hypertension: optimal treatment

ASCOT-BPLA (**A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial-**B**lood **P**ressure **L**owering **A**rm): Prevention of cardiovascular events with an antihypertensive regimen of amlodipine, adding perindopril as required, vs atenolol, adding bendroflumethiazide as required.

AUTHORS: Dahlof B, Sever P, Wedel H *et al.*

REFERENCE: *Lancet* (2005) **366**, 895–906.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

ASCOT-BPLA compared amlodipine + perindopril vs atenolol + bendroflumethiazide (BFZ) in the treatment of patients with hypertension (HTN). The trial was stopped early, because of reductions in all-cause mortality, fatal and non-fatal stroke, total cardiovascular (CV) events and procedures, and risk of developing diabetes—all in favour of the ‘newer’ regime.

Impact

In the absence of compelling reasons to prescribe β -blockers or thiazide diuretics, first-line antihypertensive therapy should now be based on the newer agents.

Aims

HTN with antihypertensive drugs significantly reduces the risk of both CV and cerebrovascular events. ASCOT-BPLA was designed to assess whether newer BP-lowering agents with metabolically favourable profiles would have a greater effect on outcome than older/conventional therapy.

Methods

Patients: 19,342 patients at multiple centres in the UK and Nordic countries.

Inclusion criteria:

- Age 40–79y;
- Untreated HTN with systolic BP (SBP) ≥ 160 mmHg \pm diastolic BP (DBP) ≥ 100 mmHg, or treated HTN with SBP ≥ 140 mmHg \pm DBP ≥ 90 mmHg;
- ≥ 3 of: left ventricular hypertrophy, type 2 diabetes mellitus (T2DM), peripheral vascular disease, previous stroke or transient ischaemic attack (TIA), σ gender, age ≥ 55 y, proteinuria or microalbuminuria, smoking, total cholesterol:HDL >6 , or family history of premature CHD.

Exclusion criteria: Previous MI, current angina, cerebrovascular accident (CVA) within 3mo, fasting triglycerides >4.5 mmol/L, HF, uncontrolled arrhythmias, clinically important biochemical/haematological abnormality.

Groups:

- Amlodipine-based regime: amlodipine (5mg, then 10mg od) + perindopril (4mg, then 8mg od) + doxazosin (4mg, then 8mg od) ($n = 9,639$).
- Atenolol-based regime: atenolol (50mg, then 100mg od) + BFZ (1.25mg, then 2.5mg od) + doxazosin (4mg, then 8mg od) ($n = 9,618$).

Follow-up: Median F/U = 5.5y (0.3% lost to F/U).

Results

Table 3.2 Endpoints

| 1° endpoint | 2° endpoints | Tertiary endpoints |
|---|-------------------------------------|-----------------------|
| Non-fatal MI, including silent MI + fatal CHD | All-cause mortality | Unstable angina |
| | Total stroke | New diabetes mellitus |
| | 1° endpoint minus silent infarction | New renal failure |
| | Coronary events and procedures | |
| | CV mortality | |
| | Non-fatal and fatal HF | |

Table 3.3 Final systolic and diastolic BP

| | Amlodipine (mmHg) | Atenolol (mmHg) | Mean difference (mmHg) | p |
|----------------|-------------------|-----------------|------------------------|---------|
| Final SBP (SD) | 136.1 (15.4) | 137.7 (17.9) | 2.7 | <0.0001 |
| Final DBP (SD) | 77.4 (9.5) | 79.2 (10.0) | 1.9 | <0.0001 |

Table 3.4 Summary of results

| 1° endpoint | Amlodipine | Atenolol | HR (95% CI) | p |
|---------------------------|------------|----------|---------------------|---------|
| Non-fatal MI + fatal CHD | 429 (5%) | 474 (5%) | 0.90 (0.79 to 1.02) | 0.1 |
| 2° endpoints | | | | |
| All-cause mortality | 738 (8%) | 820 (9%) | 0.89 (0.81 to 0.99) | 0.02 |
| Total stroke | 327 (3%) | 422 (4%) | 0.77 (0.66 to 0.89) | 0.0003 |
| Tertiary endpoints | | | | |
| Development of diabetes | 567 (6%) | 799 (8%) | 0.70 (0.63 to 0.78) | <0.0001 |

Discussion

Earlier trials had shown β -blockers and thiazide diuretics (either together or as single agents) to reduce significantly the risk of CV events in hypertensive populations, and guidelines had recommended their use as first-line therapy. ASCOT-BPLA showed that treatment of moderate-risk hypertensive patients with amlodipine (plus perindopril, if required) improved significantly CV outcomes and the risk of new-onset diabetes, compared with atenolol (plus BFZ, if required). (See Table 3.2.)

Problems

- ASCOT-BPLA did not reach its 1° endpoint and was terminated early, because of a mortality difference between the two groups.
- The trial included predominantly white ♂ subjects; ♀ patients also benefited from the amlodipine-based regime, but caution should be exercised in extrapolating the data to other ethnic groups.

Myocardial infarction: clopidogrel and metoprolol

COMMIT (C*l*o*p*i*d*o*g*r*e*l and M*e*t*o*p*r*o*l*o*l* in M*y*o*c*a*r*d*i*a*l* I*n*f*a*r*c*t*i*o*n* T*r*i*a*l): Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction.

AUTHORS: COMMIT collaborative group.

REFERENCE: *Lancet* (2005) 366, 1607–21; (2005) 366, 1622–32.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Aims

Administration of aspirin within a few hours of the onset of an acute myocardial infarction (AMI) reduces mortality, as well as the risk of reinfarction and stroke. This study aimed to test whether the addition of clopidogrel to aspirin in patients with suspected AMI would be beneficial. The role of β -blockade after AMI is established, but the use of early intravenous (IV) treatment is controversial, particularly as most previous studies were done before fibrinolytic and antiplatelet therapy became routine. Therefore, COMMIT also aimed to assess whether early β -blockade in AMI offered benefit, in addition to standard treatment.

Key message

In patients with AMI, the addition of clopidogrel to standard therapy, including aspirin, reduces mortality and the combined endpoint of death, reinfarction, and stroke. Early administration of a β -blocker after an AMI reduces the risk of reinfarction and ventricular fibrillation (VF) but increases the risk of cardiogenic shock during the first day after hospital admission.

Impact

Clopidogrel (75mg od) is indicated for up to 4wk following an AMI. β -blockers should be started after AMI, once the haemodynamic condition of the patient is stable.

Methods

Patients: 45,852 patients admitted to 1,250 hospitals in China.

Inclusion criteria: ST-segment elevation, left bundle branch block, or ST-segment depression within 24h of onset of symptoms of suspected AMI.

Exclusion criteria:

- Clear indications for, or contraindications to, the study treatments;
- Patients treated by p PCI.

Groups: All patients given aspirin (162mg od). A 2×2 factorial design:

- Clopidogrel (75mg od) ($n = 22,961$) or placebo ($n = 22,891$) for 4wk;
- IV, then oral metoprolol ($n = 22,929$) or placebo ($n = 22,923$).

Primary endpoints:

- Composite of death, reinfarction, or stroke (clopidogrel analysis);
- Composite of death, reinfarction, or cardiac arrest (metoprolol analysis);
- Death from any cause.

Secondary endpoints:

- Reinfarction;
- VF or other cardiac arrest;
- Cardiogenic shock;
- Bleeding.

Follow-up: F/U to hospital discharge or for 28d.

Results**Table 3.5** 1° endpoint

| 1° endpoint | Clopidogrel | Placebo | p |
|--------------------------------|-------------|---------|-------|
| Death, reinfarction, or stroke | 9.2% | 10.1% | 0.002 |
| Death from any cause | 7.5% | 8.1% | 0.03 |

Table 3.6 Summary of results

| 1° endpoint | Metoprolol | Placebo | p |
|--|------------|---------|--------|
| Death, reinfarction, or cardiac arrest | 9.4% | 9.9% | 0.1 |
| Death from any cause | 7.7% | 7.8% | 0.7 |
| 2° endpoint | | | |
| Reinfarction | 2.0% | 2.5% | 0.001 |
| Ventricular fibrillation | 2.5% | 3.0% | 0.001 |
| Cardiogenic shock | 2.2% | 1.7% | 0.0002 |

- The risk of bleeding (all fatal, transfused, or cerebral bleeds) was not influenced by clopidogrel—either overall in patients aged >70y or in those given fibrinolytic therapy. (See Tables 3.5 and 3.6.)

Discussion

COMMIT demonstrated that addition of clopidogrel to aspirin in patients with AMI reduced mortality and the rate of major adverse cardiovascular events. Treatment with clopidogrel for about 2wk prevented six deaths or nine adverse events (death, reinfarction, or stroke) per 1,000 patients treated, without increasing the bleeding risk. The benefit was seen across a wide range of patients and was not influenced by the use of other treatments (including fibrinolysis). The study recruited patients in China, but it is likely that the results can be applied to other populations. Although the absolute benefit of adding clopidogrel to aspirin was modest, it is now the standard management of AMI.

The study also demonstrated that early β -blockade does not reduce in-hospital mortality or the composite endpoint of death, reinfarction, or cardiac arrest. Treatment with metoprolol did reduce the risk of reinfarction and VF, but this was balanced by an increased risk of early cardiogenic shock. Thus, it is reasonable to delay β -blockade, until the haemodynamic condition of the patient is stable. Continued β -blockade as 2° prevention following hospital discharge further increases the benefit of treatment.

Problems

- A standard dose of clopidogrel was used; an initial loading dose might have had greater benefit.
- Duration of clopidogrel treatment was only 2wk; further study is required to determine whether longer-term treatment is beneficial.

Myocardial infarction: pre-hospital thrombolysis vs primary percutaneous intervention

STREAM STUDY: Strategic Reperfusion Early After Myocardial Infarction.

AUTHORS: Armstrong PW, Gerslick AH, Goldstein P et al.

REFERENCE: *N Engl J Med* (2013) **368**, 1379–87.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Pre-hospital fibrinolysis with timely coronary angiography resulted in similar clinical outcomes to 1° PCI (PPCI) in patients presenting early (<3h) with symptoms and acute ST elevation on ECG and unable to undergo PPCI within 1h. However, fibrinolysis was associated with higher rates of intracranial haemorrhage.

Impact

PPCI remains the preferred reperfusion strategy, even for patients who present early after onset of symptoms

Aims

PPCI is now widely accepted as the most effective reperfusion strategy for acute ST elevation MI (STEMI). Despite this, many patients experience long delays in accessing this treatment. If fibrinolysis with early referral for angiography resulted in similar outcomes to PPCI, it might provide a suitable alternative to overcome logistical constraints. STREAM was designed to compare pre-hospital fibrinolysis followed by coronary angiography with PPCI in patients with STEMI presenting within 3h of symptom onset.

Methods

Patients: 1,892 patients at 99 sites in 15 countries.

Inclusion criteria:

- Acute STEMI;
- ECG criteria of ST elevation of at least 2mm in two contiguous leads;
- Presentation within 3h of symptoms;
- Unable to undergo PPCI within 1h of first medical contact.

Groups:

- Fibrinolysis (weight-adjusted tenecteplase + aspirin + clopidogrel + enoxaparin);
- PPCI, as per local practice.

Follow-up: 30d (four patients lost to F/U in the fibrinolysis group, and two patients lost to F/U in the PPCI group).

Primary endpoint: Composite of death, shock, congestive cardiac failure (CCF), and reinfarction up to 30d.

Results

Table 3.7 Summary of results

| Primary endpoint | Fibrinolysis | PPCI | p |
|--|----------------------|----------------------|-------------|
| Death/shock/CCF/ reinfarction up to 30d | 116/939 (12.4%) | 135/943 (14.3%) | 0.21 |
| Total strokes | 15/939 (1.6%) | 5/946 (0.5%) | 0.03 |
| Intracranial haemorrhage | 9/939 (1.0%) | 2/946 (0.2%) (19.5%) | 0.04 |
| Any | 135 (12.4%) | 125 (11.8%) | 0.56 |
| After protocol amendment | 4/747(0.5%) | 2/758 (0.3%) | 0.45 |

Discussion

The emphasis of the trial was early randomization, and the majority of patients were randomized in the ambulance. Although time to first medical contact was similar in both groups, time to fibrinolysis was significantly lower than time to PPCI (100min vs 178min); 36.3% of patients in the fibrinolysis group were referred for emergency angiography for failure to reperfuse (<50% ST-segment resolution at 90min post-fibrinolytic drug) at a mean time delay of 2.2h. The remainder of patients receiving fibrinolysis underwent angiography at a mean delay of 17h. There was no statistical difference in the 1° composite endpoint, suggesting early reperfusion and timely coronary angiography may be a reasonable alternative to PPCI in those who cannot access PPCI within 1h. There were more strokes overall (particularly haemorrhagic) in the fibrinolysis group. This risk seemed to be greatest in patients over the age of 75y, and, following ~20% of the total recruitment, a protocol amendment recommended a 50% reduction in the dose of tenecteplase in this age group. Following this amendment, no significant difference in intracranial haemorrhage was seen. (See Table 3.7.)

Problems

- STREAM was a proof-of-concept study, and statistical tests were described as being of an exploratory nature.
- The results apply directly to patients presenting within 3h who cannot undergo PPCI within 1h of symptom onset.
- Large numbers of patients were recruited in France, which has a well-developed system of physician-led mobile intensive care unit (ICU).
- The results are not generalizable to all patients, as specific STEMI presentations, such as those with cardiogenic shock, may derive particular benefit from PPCI.
- Over a third of patients required emergency angiography for failure of reperfusion (rescue PCI).
- Mean delay to angiography in the post-thrombolysis group was relatively short and might be difficult to reproduce in real-world practice.

Myocardial infarction: thrombus aspiration

TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia)

AUTHORS: Fröbert O, Lagerqvist B, Olivecrona GK et al.

REFERENCE: *N Engl J Med* (2013) **369**, 1587–97.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with acute STEMI undergoing PCI, routine thrombus aspiration does not reduce the rates of death or hospitalization for recurrent MI at 30d, or rates of stent thrombosis or stroke.

Impact

TASTE suggests that routine thrombus aspiration has no role in patients with acute STEMI undergoing PCI.

Aims

Acute STEMI is usually caused by an occlusive thrombus within an epicardial artery. Manual thrombus aspiration through a simple intracoronary catheter can remove the thrombus and rapidly restore coronary artery flow. The TASTE trial was designed to evaluate whether routine thrombus aspiration before PCI in patients with acute STEMI reduces mortality, relative to PCI alone.

Methods

Patients: 7,259 patients at 29 Swedish, one Icelandic, and one Danish coronary intervention centres.

Inclusion criteria: Patients were eligible within 24h of onset of symptoms of STEMI (chest pain suggestive of myocardial ischaemia for at least 30min) if an ECG showed new ST-segment elevation or left bundle branch block and if PPCI was planned after coronary angiography.

Exclusion criteria:

- Need for emergency CABG;
- Inability to provide informed consent;
- Age <18y;
- Previous randomization in TASTE.

Groups:

- Thrombus aspiration and PCI ($n = 3,621$);
- Conventional PCI ($n = 3,623$).

Primary endpoint: All-cause mortality at 30d (data on mortality obtained from the Swedish national population registry).

Secondary endpoints:

- Hospitalization for recurrent MI;
- Composite of all-cause death or recurrent MI;
- Stent thrombosis;
- Target vessel revascularization;
- Stroke or neurologic complications;
- HF.

Follow-up: 30d.

Results

Table 3.8 Summary of results

| | Thrombus aspiration and PCI | PCI only | p |
|--|--------------------------------|----------|------|
| 1° endpoint | | | |
| All-cause death | 2.8% | 3.0% | 0.63 |
| 2° endpoints at 30d | | | |
| Rehospitalization due to reinfarction | 0.5% | 0.9% | 0.09 |
| All-cause death or reinfarction | 3.3% | 3.9% | 0.23 |
| Stent thrombosis | 0.2% | 0.5% | 0.06 |
| Target vessel revascularization | 1.8% | 2.2% | 0.27 |
| Target lesion revascularization | 1.2% | 1.6% | 0.16 |
| 2° endpoints during index hospitalization | | | |
| Stroke or neurologic complication | 0.5% | 0.5% | 0.87 |
| HF | 6.8% | 6.5% | 0.60 |

Discussion

The role of routine thrombus aspiration in patients with acute STEMI undergoing PCI is controversial. The TAPAS trial (*N Engl J Med* (2008) 358, 557–67; *Lancet* (2008) 371, 1915–20) reported that thrombus aspiration before PCI reduced mortality at 1y, when compared with PCI without thrombus aspiration, but TAPAS was underpowered for this outcome. The TASTE trial showed that PCI with routine thrombus aspiration had no effect on all-cause mortality, compared with PCI alone. In a F/U report, thrombus aspiration had no effect on the rates of death and rehospitalization for MI or stent thrombosis at 1y. (See Table 3.8.)

Problems

- The trial endpoints were based on investigators reporting with no formal endpoint adjudication, and, in an open-label trial, this might introduce bias.
- The mortality rate at 30d was lower than expected, and the trial sample size had to be increased during enrolment. In a registry of patients who were not randomized, 30-d mortality exceeded 10%, suggesting that the trial systematically excluded high-risk patients.
- The results of the larger TOTAL trial ($n = 10,700$) of routine aspiration thrombectomy are awaited (NCT01149044).

Non-ST elevation acute coronary syndrome: fondaparinux

OASIS 5: The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators.

AUTHORS: Yusuf S, Mehta S, Chrolavicius S *et al.*

REFERENCE: *N Engl J Med* (2006) **354**, 1464–76.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with non-ST-segment elevation acute coronary syndromes (ACS), fondaparinux has similar efficacy to enoxaparin but reduces bleeding and longer-term mortality.

Impact

In patients presenting with ACS, replacing enoxaparin with fondaparinux reduces early bleeding complications and longer-term mortality. Fondaparinux is associated with an increased risk of catheter-related thrombosis, and additional anticoagulation at the time of invasive cardiac procedures is advised.

Aims

In patients with ACS, combination use of antiplatelet and antithrombotic agents, coupled with invasive coronary revascularization strategies, reduces ischaemic events and improves outcomes, but at an increased risk of bleeding. OASIS 5 aimed to compare the efficacy and safety of fondaparinux and enoxaparin in patients with non-ST-segment elevation ACS.

Methods

Patients: 20,078 patients at 576 centres in 41 countries.

Inclusion criteria:

- Unstable angina or non-STEMI (NSTEMI) within 24h of symptom onset and ≥ 2 of:
 - Age at least 60y;
 - Elevated troponin or CK-MB;
 - ECG changes of ischaemia.

Exclusion criteria:

- Contraindication to enoxaparin;
- Recent haemorrhagic stroke;
- Indication for anticoagulation other than ACS;
- Renal impairment (creatinine >265 micromol/L).

Groups:

- Enoxaparin 1mg/kg subcutaneously (SC) twice daily (bd): $n = 10,021$;
- Fondaparinux 2.5mg od: $n = 10,057$;
- All patients managed with standard medical therapy and cardiac catheterization performed, as clinically indicated;
- Mean duration of treatment: 5d for each study drug.

Primary efficacy endpoint: Composite of death, MI, or refractory ischaemia at 9d.

Primary safety endpoint: Major bleeding at 9d.

Composite risk–benefit endpoint: Death, MI, refractory ischaemia, or bleeding at 9d.

Secondary endpoints: As above at 30d and 180d.

Follow-up: 90–180d.

Results

Table 3.9 Summary of results

| Endpoint | Enox. | Fonda. | HR (95% CI) | p |
|----------------------------------|-------|--------|------------------|-------------------------|
| Death/MI/ischaemia 9d | 5.7% | 5.8% | 1.01 (0.90–1.13) | 0.007 (non-inferiority) |
| Major bleeding 9d | 4.1% | 2.2% | 0.52 (0.44–0.61) | <0.001 |
| Death/MI/ischaemia/bleeding 9d | 9.0% | 7.3% | 0.81 (0.73–0.89) | <0.001 |
| Death/MI/ischaemia 30d | 8.6% | 8.0% | 0.93 (0.83–1.02) | 0.13 |
| Major bleeding 30d | 5.0% | 3.1% | 0.62 (0.54–0.72) | <0.001 |
| Death/MI/ischaemia/bleeding 30d | 12.4% | 10.2% | 0.82 (0.75–0.89) | <0.001 |
| Death/MI/ischaemia 180d | 13.2% | 12.3% | 0.93 (0.86–1.00) | 0.06 |
| Major bleeding 180d | 5.8% | 4.3% | 0.72 (0.64–0.82) | <0.001 |
| Death/MI/ischaemia/bleeding 180d | 17.1% | 15% | 0.86 (0.81–0.93) | <0.001 |

Discussion

In OASIS 5, fondaparinux was non-inferior to enoxaparin in the short term but associated with a significantly reduced rate of bleeding. Over the longer term, fondaparinux was associated with lower morbidity and mortality. The effects appeared to be consistent across all subgroups. In addition, a significant reduction in stroke was seen in the fondaparinux group at both 30 and 180d. A number of studies have shown bleeding to be associated with an adverse prognosis in patients with ACS. Fondaparinux is recommended as the anticoagulant of choice by several guideline groups. (See Table 3.9.)

Problems

- There was an increased incidence of guide catheter thrombosis in the fondaparinux group (29 episodes (0.9%) vs eight episodes (0.3%) with enoxaparin). Following reports of catheter-related thrombus, a protocol amendment was made, allowing operators to give an open-label bolus of unfractionated heparin (UFH) at the time of PCI, in addition to the study drug. This appeared to abolish the incidence of catheter-related thrombosis in both study groups, with no excess bleeding seen in the fondaparinux-treated group.

Further reading

Eur Heart J (2003) 24, 1815–23.

Non-ST elevation acute coronary syndrome: ticagrelor

PLATO STUDY (PLATelet inhibition and patient Outcomes).

AUTHORS: Wallentin L, Becker RC, Budjai A et al.

REFERENCE: *N Engl J Med* (2009) **361**, 1045–57.

STUDY DESIGN: Multicentre, randomized, double-blinded controlled trial.

EVIDENCE LEVEL: 1b.

Key message

In patients presenting with ACS (with or without ST-segment elevation), treatment with ticagrelor, rather than clopidogrel, significantly reduces the risk of death from vascular causes, MI, and stroke, without increasing the risk of major bleeding. Non-procedure-related bleeding is increased.

Impact

Ticagrelor is now widely used in clinical practice and is recommended by clinical guideline groups for the management of patients with ACS, including those undergoing PPCI for acute STEMI.

Aims

Conventional treatment for ACS includes a combination of dual antiplatelet therapy with aspirin and clopidogrel. Clopidogrel is a prodrug, and conversion to the active metabolite delays the onset of action. In addition, some patients are resistant to the effects of clopidogrel, increasing the risk of thrombosis/stent thrombosis and MI. PLATO was performed to determine whether the direct-acting, reversible oral adenosine diphosphate (ADP) P2Y₁₂ receptor antagonist ticagrelor was superior to clopidogrel in patients with ACS without a significantly higher risk of bleeding.

Methods

Patients: 18,624 patients from 862 centres in 43 countries.

Inclusion criteria:

- ACS with/without ST elevation within 24h of symptom onset;
- If no ST elevation on ECG, then at least two of the following:
 - ST-segment change indicating ischaemia;
 - Positive biomarker indicating myocardial necrosis, or one additional risk factor (age >60; previous MI/CABG; known CAD; previous TIA/CVA).

Exclusion criteria:

- Any contraindication to clopidogrel;
- Fibrinolysis within 24h prior to randomization;
- Need for oral anticoagulation;
- Increased risk of bradycardia;
- Concomitant therapy with a strong P450 3A inhibitor/inducer.

Groups:

- Aspirin + ticagrelor 180mg loading and 90mg bd maintenance;
- Aspirin and either 300mg or 600mg loading + 75mg od maintenance.

Follow-up: 12mo.

Primary endpoint: Death from vascular causes, MI, or CVA.

Results

Table 3.10 Summary of results

| 1° endpoint | Ticagrelor | Clopidogrel | p |
|--|------------|-------------|--------|
| Composite of death from vascular causes, MI, or stroke | 9.8% | 11.7% | <0.001 |
| 2° endpoints | | | |
| MI | 5.8% | 6.9% | 0.005 |
| Death from vascular causes | 4.0% | 5.1% | 0.001 |
| Stroke | 1.5% | 1.3% | 0.22 |
| Death any cause | 4.5% | 5.9% | <0.001 |
| Definite stent thrombosis | 1.3% | 1.9% | 0.009 |
| 1° safety endpoints | | | |
| Major bleeding | 11.6% | 11.2% | 0.43 |
| Life-threatening bleeding | 5.8% | 5.8% | 0.70 |

Discussion

In the quest for more potent and consistent antiplatelet agents for use in patients with ACS, increased platelet inhibition has been associated with increased rates of bleeding, especially in the context of PCI. In PLATO, patients presenting with or without ST elevation and managed with both invasive and non-invasive strategies were included. Ticagrelor was associated with a reduced risk of the composite outcome of death from vascular causes, MI, and stroke, but also for overall mortality. This was not associated with an increased risk of major, life-threatening, or fatal bleeding. (See Table 3.10.)

Problems

- Concerns have arisen in that many patients in the clopidogrel arm did not receive the higher loading dose of 600mg conventionally given to patients prior to urgent/emergency coronary intervention.
- Variations in efficacy in a subgroup analysis of North American patients have been reported, the cause of which is unclear but may be related to the higher dose of aspirin commonly used in this population.
- Many patients were on clopidogrel before randomization, but the impact of this treatment on the results of the trial is unknown. Whether this was an advantage, as they were already loaded, or suggested a degree of clopidogrel non-responder status is unknown.
- Higher overall major bleeding rates seen in the clopidogrel arm of PLATO than other trials (e.g. TRITON). In PLATO, patients randomized in the catheter laboratory, and so patients with higher bleeding risk may have been excluded.

Further reading

Circulation (2010) 122, 2131–41.

Lancet (2010) 375, 283–93.

N Engl J Med (2007) 357, 2001–15.

Non-ST elevation acute coronary syndrome: enoxaparin

ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events) study: A comparison of low-molecular-weight heparin (LMWH) with UFH for unstable CAD.

AUTHORS: Cohen M, Demers C, Gurfinkel E et al.

REFERENCE: *N Engl J Med* (1997) 337, 447–52.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Antithrombotic therapy with SC enoxaparin and aspirin is more effective than continuous IV UFH and aspirin at reducing ischaemic events in patients with non-ST elevation ACS.

Impact

Enoxaparin is administered routinely in the acute management of patients with non-ST elevation ACS.

Aims

Several small trials had suggested that IV UFH reduced the risk of ischaemic events in patients with non-ST elevation ACS. LMWHs have several potential advantages over UFH, including a predictable anticoagulant effect and no requirement for anticoagulant monitoring. This study was designed to compare the efficacy and safety of enoxaparin and UFH in patients with non-ST elevation ACS.

Methods

Patients: 3,171 patients at 176 hospitals in ten countries.

Inclusion criteria: Eligible patients had angina within the previous 24h, associated with one of the following:

- ST-segment depression of ≥ 0.1 mV, transient ST-segment elevation, or T-wave changes in two contiguous leads;
- Previous MI or revascularization;
- Previous invasive/non-invasive investigations suggesting ACS.

Exclusion criteria:

- Left bundle branch block or persistent ST elevation;
- Contraindication to anticoagulation;
- Creatinine clearance < 30 mL/min.

Groups:

- Enoxaparin: 1mg/kg body weight enoxaparin SC every 12h, with an IV placebo bolus and infusion ($n = 1,607$);
- UFH: SC placebo injections and an IV bolus of UFH (usually 5,000U), followed by continuous heparin infusion at a dose determined by the activated partial thromboplastin time (APTT) ($n = 1,564$).

Primary endpoint:

- Composite of death, non-fatal MI, and recurrent angina at 48h, 14d, and 30d.

Secondary endpoints:

- Rate of death and non-fatal MI at 48h, 14d, and 30d;
- Major and minor haemorrhage.

Results**Table 3.11** Summary of results

| Primary endpoint | UFH | Enoxaparin | <i>p</i> |
|----------------------------|-------|------------|----------|
| Composite primary endpoint | 19.8% | 16.6% | 0.02 |
| Death (at 14d) | 2.3% | 2.2% | 0.9 |
| MI (at 14d) | 3.8% | 2.7% | 0.06 |
| Recurrent angina (at 14d) | 15.5% | 12.9% | 0.03 |
| Primary endpoint (at 30d) | 23.3% | 19.8% | 0.02 |
| Death/MI (at 30d) | 7.7% | 6.2% | 0.08 |
| Revascularization (at 30d) | 32.2% | 27.0% | 0.001 |
| Bleeding | | | |
| Any bleeding (at 30d) | 14.2% | 18.4% | 0.001 |
| Major bleeding (at 30d) | 7.0% | 6.5% | 0.6 |

Discussion

ESSENCE demonstrated that enoxaparin was more effective than UFH in reducing ischaemic events at 14d (sustained at 30d) in patients with non-ST elevation ACS. The difference in the composite endpoint was driven mainly by a reduction in the risk of recurrent angina, but, at 30d, there was a trend for a lower rate of death or MI in the enoxaparin group. Enoxaparin was associated with an increased risk of minor, but not major, bleeding. A meta-analysis of trials of enoxaparin vs UFH included 21,946 patients with non-ST elevation ACS—enoxaparin prevented ten deaths or non-fatal MI per 1,000 patients, without increasing bleeding risk (*Eur Heart J* (2007) **28**, 2077–86). (See Table 3.11.)

Problems

- The beneficial effects of enoxaparin in non-ST elevation ACS cannot be translated to other LMWHs with different pharmacological profiles.
- Most of the trials of LMWH were conducted before the widespread use of thienopyridines (ticlopidine or clopidogrel) or glycoprotein IIb/IIIa receptor antagonists.
- Although enoxaparin is widely used in the management of patients with non-ST elevation ACS, novel antithrombins (including bivalirudin and fondaparinux) may be associated with a lower risk of bleeding.

Non-ST elevation acute coronary syndrome: clopidogrel

CURE (Clopidogrel in Unstable angina to prevent Recurrent Events): Effects of clopidogrel, in addition to aspirin, in patients with ACS without ST-segment elevation.

AUTHORS: CURE Trial Investigators.

REFERENCE: *N Engl J Med* (2001) **345**, 494–502.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Clopidogrel, in addition to aspirin, confers CV benefits in patients with ACS, without ST-segment elevation, but increases the risk of major bleeding.

Impact

Clopidogrel (75mg od) is prescribed routinely in patients with non-ST-segment elevation ACS.

Aims

ACS is caused by erosion or rupture of an atherosclerotic plaque with subsequent platelet-mediated coronary thrombosis. Aspirin irreversibly inhibits cyclo-oxygenase (COX)-dependent platelet aggregation and reduces the risk of death, MI, and recurrent ischaemia in patients with unstable CAD. Clopidogrel is a thienopyridine derivative which inhibits ADP-induced platelet aggregation. This study aimed to test whether the addition of clopidogrel to aspirin could improve outcome in patients with non-ST-segment elevation ACS.

Methods

Patients: 12,562 patients at 482 centres in 28 countries.

Inclusion criteria:

- Patients presenting within 24h of onset of symptoms of ACS without ST-segment elevation;
- The protocol was amended after the first 3,000 patients had been recruited. Thereafter, patients were only enrolled if they had ECG changes or elevation of a serum cardiac marker or enzyme.

Exclusion criteria:

- Contraindication to antithrombotic treatment;
- High risk of bleeding;
- Severe HF;
- Oral anticoagulant therapy;
- Coronary revascularization within previous 3mo;
- Glycoprotein IIb/IIIa receptor antagonists in previous 3d.

Groups: Mean duration of therapy 9mo. Aspirin (75–325mg od) was given to all patients:

- Clopidogrel (300mg loading, then 75mg od) ($n = 6,259$);
- Placebo ($n = 6,303$).

Primary endpoint:

- CV death, non-fatal MI, or stroke;
- CV death, MI, stroke, or refractory ischaemia.

Secondary endpoint: Major bleeding.

Follow-up: At 3-monthly intervals for a mean of 9mo.

Results

Table 3.12 Summary of results

| Endpoint | Clopidogrel | Placebo | <i>p</i> |
|--|-------------|---------|----------|
| CV death, MI, or stroke | 9.3% | 11.4% | <0.001 |
| CV death, MI, stroke, refractory ischaemia | 16.5% | 18.8% | <0.001 |
| CV death | 5.1% | 5.5% | ns |
| MI | 5.2% | 6.7% | <0.05 |
| Stroke | 1.2% | 1.4% | ns |
| Refractory ischaemia | 8.7% | 9.3% | ns |
| Minor bleeding | 5.1% | 2.4% | <0.001 |
| Major bleeding | 3.7% | 2.7% | 0.001 |
| Life-threatening bleeding | 2.2% | 1.8% | 0.1 |

Discussion

Addition of clopidogrel to aspirin in patients with non-ST-segment elevation ACS reduced the risk of MI, with a trend towards lower rates of stroke and CV death. Clopidogrel also reduced the risk of recurrent ischaemia during initial hospitalization. These benefits emerged within 24h of starting treatment but should be balanced against an increased risk of minor and major bleeding. Treatment of 1,000 patients with clopidogrel for 9mo will prevent 28 adverse CV events (CV death, MI, or stroke) in 22 patients but will cause an additional ten major bleeds (of which six will require transfusion and four may be life-threatening). Overall, treatment with clopidogrel results in net clinical benefit and is now part of the standard management of patients with non-ST elevation ACS. (See Table 3.12.)

Problems

- The loading dose of clopidogrel was 300mg, but higher loading doses (600mg) have been shown to have more rapid antiplatelet effect and possible additional clinical benefit.
- Although clopidogrel was continued for a mean of 9mo, most benefit accrued within the first 3mo. Further research is required to ascertain the optimal duration of treatment.
- Treating all patients with non-ST-segment elevation ACS with clopidogrel is expensive, but economic analyses confirm that dual antiplatelet therapy for 9mo after presentation is cost-effective.

Non-ST elevation acute coronary syndrome: timing of intervention

TIMACS (Timing of Intervention in Acute Coronary Syndrome).

AUTHORS: Mehta SR, Granger CB, Boden WE et al.

REFERENCE: *N Engl J Med* (2009) **360**, 2165–75.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A routine early invasive strategy (coronary angiography within 24h of randomization) in patients with non-ST-segment elevation ACS does not reduce the risk of death, MI, or stroke at 6mo but reduces the risk of refractory ischaemia, relative to a delayed invasive strategy (coronary angiography ≥ 36 h after randomization).

Impact

TIMACS provides evidence that routine early invasive strategy in patients with non-ST-segment elevation ACS reduces the risk of refractory ischaemia and may be particularly beneficial in high-risk patients.

Aims

Randomized trials have demonstrated that a routine invasive strategy in patients with non-ST-segment elevation ACS improves outcomes, when compared with a selective invasive strategy, but the optimal timing of the routine invasive procedure has not been established. TIMACS compared an early invasive strategy with a delayed invasive strategy in patients with non-ST-segment elevation ACS.

Methods

Patients: 3,031 patients with ACS without ST-segment elevation at multinational centres.

Inclusion criteria:

- Unstable angina or MI without ST-segment elevation within 24h of symptom onset and two of three criteria indicating increased risk (age ≥ 60 y; cardiac biomarker above the upper limit of the normal; ECG evidence of ischaemia).

Exclusion criteria: Unsuitable for revascularization.

Groups:

- Routine early intervention ($n = 1,593$);
- Delayed intervention ($n = 1,438$).

Primary endpoint: Composite of death, new MI, or stroke at 6mo.

Secondary endpoints:

- Composite of death, MI, or refractory ischaemia at 6mo.
- Composite of death, MI, stroke, refractory ischaemia, or repeat intervention at 6mo.

Follow-up: 6mo.

Results

Table 3.13 Summary of results

| | Early intervention | Delayed intervention | HR (95% CI) | p |
|---|--------------------|----------------------|---------------------|--------|
| Primary endpoint | | | | |
| Death, MI, or stroke | 9.6% | 11.3% | 0.85 (0.68–1.06) | 0.15 |
| Death, MI, or stroke, and GRACE score 0–140 | 7.6% | 6.7% | 1.12 (0.81–1.56) | * |
| Death, MI, or stroke, and GRACE score >140 | 13.9% | 21.0% | 0.65 (0.48–0.89) | * |
| Secondary endpoints at 6mo | | | | |
| Death, MI, or refractory ischaemia | 9.5% | 12.9% | 0.72 (0.58–0.89) | 0.003 |
| Refractory ischaemia | 1.0% | 3.3% | 0.30 (0.17–0.54) | <0.001 |
| Death, MI, stroke, refractory ischaemia, or repeat intervention | 16.6% | 19.5% | 0.84 (0.71–0.99) | 0.04 |
| Secondary endpoints at 30d | | | | |
| Death, MI, or stroke | 6.7% | 7.6% | 0.88 (0.67–1.15) | 0.34 |
| Death, MI, or refractory ischaemia | 6.6% | 9.3% | 0.70 (0.54–0.90) | 0.006 |
| Refractory ischaemia | 1.0% | 3.1% | 0.30 (0.17–0.55) | <0.001 |

*p for interaction = 0.01.

Discussion

In the TIMACS trial, an early invasive strategy (coronary angiography ≤ 24 h of randomization) did not reduce the risk of the composite outcome of death, new MI, or stroke, but did reduce the risk of refractory ischaemia, relative to a delayed invasive strategy. In a subgroup analysis, early invasive strategy in patients with a high baseline GRACE score was associated with lower risk of both the composite 1° outcome and refractory ischaemia. (See Table 3.13.)

Problems

- The main benefit of early invasive strategy was to reduce the risk of refractory ischaemia, and overall there was no evidence of an effect on other endpoints.
- The trial recruited over 3,000 patients but lacks statistical power, especially for mortality.
- A subgroup analysis suggests that an early invasive strategy may be beneficial in patients with a high baseline GRACE score. The cost efficacy of a strategy of risk stratification and routine early invasive treatment in high-risk patients with non-ST-segment elevation ACS requires confirmation in further appropriately powered randomized trials.

Coronary artery disease: percutaneous intervention

COURAGE (Clinical Outcomes Utilising Revascularisation and Aggressive drug Evaluation) trial: Optimal medical therapy, with or without PCI, for stable CAD.

AUTHORS: Boden W, O'Rourke R, Teo K et al.

REFERENCE: *N Engl J Med* (2007) 356, 1503–16.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

COURAGE assessed the impact of PCI (including the use of bare-metal coronary stents) on prognosis in patients with stable CAD. In patients on optimal medical therapy, an initial strategy of routine PCI does not reduce the risk of death, MI, or other CV events, when compared with a strategy of selective PCI for angina.

Impact

PCI with bare-metal coronary stents does not influence the risk of death or MI in patients with stable CAD who are on optimal medical therapy. PCI should be reserved for patients with limiting angina and is not indicated in patients with asymptomatic or mildly symptomatic CAD.

Aims

Although coronary balloon angioplasty is an effective treatment for chronic stable angina, it has never been shown to improve mortality or risk of MI in these patients. This trial aimed to compare an initial strategy of optimal medical therapy and routine PCI (including coronary stents), with an initial strategy of optimal medical therapy alone.

Methods

Patients: 2,287 patients at 50 centres in the USA.

Inclusion criteria:

- Stable CAD;
- Canadian Cardiovascular Society class I–III angina;
- Significant stenosis in ≥ 1 proximal epicardial coronary artery with objective evidence of myocardial ischaemia or typical angina;
- Coronary anatomy suitable for PCI;
- Ejection fraction (EF) $\geq 30\%$.

Exclusion criteria:

- Persistent Canadian Cardiovascular Society class IV angina;
- Markedly positive exercise test (within stage 1 of the Bruce protocol);
- Revascularization within the previous 6mo.

Groups: All patients given angiotensin-converting enzyme inhibitors (ACE-Is), anti-ischaemic, antiplatelet, and lipid-lowering therapy:

- Optimal medical therapy ($n = 1,138$);
- Optimal medical therapy and PCI ($n = 1,149$).

Follow-up: Mean F/U 4.6y.

Primary endpoint: Composite of death from any cause and non-fatal MI.

Secondary endpoints:

- Composite of death, MI, and stroke;
- Hospitalization for unstable angina (with negative biomarkers);
- Canadian Cardiovascular Society angina class.

Results

Table 3.14 Summary of results

| Primary endpoint | Optimal medical and PCI | Optimal medical | p |
|-------------------------------------|-------------------------|-----------------|--------|
| Death or non-fatal MI | 19.0% | 18.5% | 0.6 |
| Secondary endpoints | | | |
| Death | 7.6% | 8.3% | |
| MI | 13.2% | 12.3% | 0.3 |
| Death, MI, stroke | 20.0% | 19.5% | 0.6 |
| Hospitalization for unstable angina | 12.4% | 11.8% | 0.6 |
| Additional revascularization | 21.1% | 32.6% | <0.001 |
| Angina-free at 3y | 72% | 67% | 0.02 |
| Angina-free at 5y | 74% | 72% | ns |

Discussion

Previous trials had shown that coronary balloon angioplasty was an effective treatment for stable angina but did not influence the risk of death or MI. COURAGE confirmed these findings for PCI with bare-metal coronary stents. More patients in the PCI group were free from angina, with lower use of anti-anginal medications, but this difference reduced over time, probably because of additional revascularization and intensive control of vascular risk factors in the optimal medical therapy arm. (See Table 3.14.)

Problems

- The trial compared two initial treatment strategies, but, following assignment, 32.6% of the medical group underwent a revascularization procedure (for severe or unstable symptoms), and 21.1% of the PCI group had a repeat revascularization procedure (probably for restenosis).
- Patients were enrolled over a period of 4.5y. During this time, there were advances in both medical and interventional treatments for CAD. Importantly, COURAGE was conducted before the introduction of drug-eluting stents, but available data indicate that these do not confer prognostic benefit, when compared with bare-metal stents (BMS).

Coronary artery disease: revascularization vs medical care in diabetes

BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes).

AUTHORS: The BARI 2D Study Group.

REFERENCE: *N Engl J Med* (2009) **360**, 2503–15.

STUDY DESIGN: RCT (2×2 factorial design).

EVIDENCE LEVEL: 1b.

Key message

In patients with T2DM and angiographically documented CAD, 5-y survival and rates of major CV events do not differ between strategies of prompt revascularization and contemporary medical therapy, compared with contemporary medical therapy alone, or between insulin sensitization and insulin provision.

Impact

The results of BARI-2D suggest that patients with CAD and T2DM can be managed by an initial strategy of medical therapy and that routine insulin provision does not improve CV outcomes.

Aims

BARI-2D was designed to compare prompt revascularization and contemporary medical therapy with medical therapy alone in patients with T2DM and CAD. The study also compared insulin sensitization with insulin provision.

Methods

Patients: 2,368 patients at 49 clinical sites in the USA, Canada, Brazil, Mexico, the Czech Republic, and Austria.

Inclusion criteria:

- T2DM or an elevated blood glucose level;
- CAD on angiography ($\geq 50\%$ stenosis of a major epicardial coronary artery, associated with a positive stress test, or $\geq 70\%$ stenosis of a major epicardial coronary artery and classic angina);
- Eligible for elective PCI or CABG.

Exclusion criteria:

- Requirement for immediate revascularization;
- Left main coronary disease;
- Creatinine level $> 2.0 \text{ mg/dL}$ (177 micromol/L);
- Glycosylated haemoglobin (Hb) level $> 13.0\%$;
- Class III or IV HF;
- Hepatic dysfunction;
- PCI or CABG within the previous 12 mo.

Groups: Randomization stratified, according to method of revascularization (PCI or CABG) determined by the responsible physician:

- Prompt coronary revascularization + medical therapy ($n = 1,176$);
- Medical therapy alone ($n = 1,192$).

- Insulin sensitization with thiazolidinediones/metformin ($n = 1,183$)
- Insulin provision ($n = 1,185$)

Primary endpoint: Death from any cause.

Secondary endpoints: Composite of death, MI, or stroke.

Follow-up: Mean 5.3y.

Results

Table 3.15 Summary of results

| | Revascularization + medical therapy | Medical therapy | <i>p</i> |
|------------------------------|--|-------------------|----------|
| 5-y survival | | | |
| All patients | 88.3% | 87.8% | 0.97 |
| Major CV events at 5y | | | |
| All patients | 77.2% | 75.9% | 0.70 |
| | Insulin sensitization | Insulin provision | <i>p</i> |
| 5-y survival | | | |
| All patients | 88.2% | 87.9% | 0.89 |
| Major CV events at 5y | | | |
| All patients | 77.7% | 75.4% | 0.13 |

Discussion

Patients with T2DM and angiographically documented CAD are at high CV risk, but few large randomized trials have addressed the management of this patient group. In the BARI-2D trial, prompt revascularization had no beneficial effect on survival rate or the rate of major CV events at 5y, relative to an initial strategy of continued medical therapy. In a subgroup analysis, patients in the prospectively defined CABG stratum who were assigned to revascularization had a lower rate of major CV events than patients assigned to medical therapy. Overall, there was no difference in CV outcomes between patients assigned to insulin sensitization and insulin provision. (See Table 3.15.)

Problems

- Recruited patients with CAD and T2DM who were considered suitable for revascularization or continued medical therapy and high-risk patients were systematically excluded. Results of the trial are therefore not generalizable to all patients with CAD and T2DM.
- The trial failed to recruit the target of 2,800 patients, and, although the duration of F/U was extended, the trial is relatively underpowered.
- During F/U, 42% of patients initially assigned to medical therapy underwent a revascularization procedure.
- Approximately one-third of patients in the PCI stratum were treated with a first-generation drug-eluting stent, but the use of later-generation drug-eluting stents has improved outcomes in patients treated by PCI.
- At 3-y F/U, over half of the insulin sensitization group were taking rosiglitazone, but this drug is no longer licensed for use in Europe.

Coronary artery disease: PCI vs CABG in diabetes

FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease).

AUTHORS: Farkouh ME, Domanski M, Sleeper LA et al.

REFERENCE: *N Engl J Med* (2012) 367, 2375–84.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with diabetes and multivessel CAD, CABG significantly reduces the rates of death and MI but increases the rate of stroke, compared with PCI.

Impact

International guidelines recommend CABG as the preferred revascularization strategy in patients with medically treated diabetes and multivessel CAD.

Aims

To evaluate the role of PCI using drug-eluting stents, compared with CABG, in patients with diabetes and multivessel CAD who were managed with contemporary medical therapy.

Methods

Patients: 1,900 patients at 140 international centres.

Inclusion criteria: Angiographically confirmed multivessel CAD with stenosis of >70% in two or more major epicardial vessels, involving at least two separate coronary artery territories and without left main coronary stenosis.

Groups:

- PCI ($n = 953$);
- CABG ($n = 947$).

Primary endpoint: Composite of all-cause death, non-fatal MI, and non-fatal stroke.

Secondary endpoints:

- Rate of major adverse CV and cerebrovascular events 30d and 12mo after the procedure;
- Components of the 1° outcome;
- Repeat revascularization;
- Annual all-cause mortality;
- CV mortality.

Follow-up: Median F/U time 3.8y (interquartile range 2.5–4.9y).

Results

Table 3.16 Summary of results

| | PCI | CABG | <i>p</i> |
|-------------------------------|-----|------|----------|
| Total number of events | | | |
| Primary endpoint | 205 | 147 | 0.005 |
| Death from any cause | 118 | 86 | 0.049 |
| MI | 99 | 48 | <0.001 |
| Stroke | 22 | 37 | 0.03 |
| CV death | 75 | 55 | 0.12 |

Discussion

The optimal revascularization strategy for patients with medically treated diabetes and multivessel CAD is controversial. In a meta-analysis of older trials of myocardial revascularization, CABG was associated with a survival advantage over PCI (using balloon angioplasty or BMS) in patients with diabetes (*Lancet* (2009) 373, 1190–7). The FREEDOM trial is the largest single trial of revascularization strategies in patients with diabetes and compared CABG with PCI, using first-generation drug-eluting stents. Over 5y, CABG was associated with lower rates of death and MI, but significantly more strokes, most of which occurred within 30d after revascularization. (See Table 3.16.)

Problems

- The majority of patients in the PCI arm of the trial were treated with first-generation sirolimus-eluting or paclitaxel-eluting stents, but newer drug-eluting stents are associated with better clinical outcomes, including lower rates of stent thrombosis.
- During the recruitment phase, 32,966 patients were screened, but only 1,900 patients (5.8%) were enrolled in the trial, and 83% had 3-vessel disease. The results of FREEDOM therefore do not relate directly to all patients with multivessel disease and diabetes being considered for myocardial revascularization.
- With 1,900 participants, the trial has limited statistical power, especially for components of the composite 1° outcome. The Kaplan–Meier curves for mortality only start to separate after 2y of F/U, and the absolute extension of survival over 5y from CABG, relative to PCI, is modest (a few months). This benefit has to be balanced against the morbidity associated with surgical revascularization, including an increased risk of stroke.
- Further randomized trials of CABG vs PCI using contemporary drug-eluting stents are required to confirm the superiority of CABG in patients with diabetes and multivessel disease, but new therapeutic strategies are required to substantially improve the overall outcome of this high-risk patient group.

Coronary artery disease: PCI vs CABG in multivessel disease

SYNTAX (SYNergy between PCI with TAXus and cardiac surgery).

AUTHORS: Serruys PW, Morice M-C, Kappetein AP et al.; Mohr FW, Morice M-C, Kappetein AP et al.

REFERENCE: *N Engl J Med* (2009) **360**, 961–72; *Lancet* (2013) **381**, 629–38.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Revascularization with CABG results in lower rates of major adverse cardiac or CV events than with PCI.

Impact

The SYNTAX trial has influenced guidelines in Europe and North America, which recommend selection of the revascularization strategy on the basis of the severity of CAD assessed by the SYNTAX score.

Aims

To compare PCI (with paclitaxel-eluting coronary stents) and CABG in patients with previously untreated 3-vessel disease and/or left main CAD.

Methods

Patients: 1,800 patients at 85 sites in 17 countries in Europe and the USA.

Inclusion criteria:

- Untreated 3-vessel disease or left main CAD (alone or with 1-, 2-, or 3-vessel disease) with $\geq 50\%$ stenosis in at least one target vessel;
- Equivalent revascularization considered possible with either CABG or PCI;
- Stable or unstable angina, or atypical chest pain, or asymptomatic with positive evidence of myocardial ischaemia.

Exclusion criteria:

- Previous PCI or CABG;
- Acute MI;
- Requirement for concomitant cardiac surgery.

Groups:

- CABG ($n = 897$);
- PCI ($n = 903$).

Primary endpoint: Composite of death from any cause, stroke, MI, or repeat revascularization (major adverse cardiac and cerebrovascular events, MACCE).

Secondary endpoints:

- MACCE analysed by SYNTAX score (the SYNTAX score assesses anatomical disease severity, with higher scores indicating more complex coronary disease);

- Death from any cause;
- MI;
- Death or stroke or MI;
- Repeat revascularization

Follow-up: 1 and 5y.

Results

Table 3.17 Summary of results

| | CABG | PCI | <i>p</i> |
|----------------------------------|-------|-------|----------|
| Primary endpoint | | | |
| MACCE at 1y | 12.4% | 17.8% | 0.002 |
| MACCE at 5y | 26.9% | 37.3% | <0.0001 |
| Secondary endpoints at 5y | | | |
| Death from any cause | 11.4% | 13.9% | 0.10 |
| MI | 3.8% | 9.7% | <0.0001 |
| Stroke | 3.7% | 2.4% | 0.09 |
| Death or stroke or MI | 16.7% | 20.8% | 0.03 |
| Repeat revascularization | 13.7% | 25.9% | <0.0001 |

Discussion

The optimal revascularization strategy for patients with multivessel CAD has been debated for several decades. Randomized trials of CABG vs PCI in the pre-stent (balloon angioplasty) era enrolled relatively low-risk patients and demonstrated that PCI was associated with a greater requirement for additional revascularization procedures and less effective relief of angina than CABG. Although BMS improved the results of PCI, these devices were associated with a risk of stent thrombosis and restenosis, which impaired long-term clinical outcome. The introduction of drug-eluting stents improved the results of PCI and reignited the debate about the optimal method of revascularization, especially in patients with complex multivessel disease. The SYNTAX trial suggests that CABG is associated with a lower risk of MACCE over 5y. The benefit of CABG appeared to be confined to patients with high baseline SYNTAX scores. (See Table 3.17.)

Problems

- In contemporary PCI practice, first-generation paclitaxel-eluting stents have been superseded by newer-generation everolimus-eluting stents that are associated with better clinical outcomes.
- SYNTAX was designed as a non-inferiority trial and, with 1,800 patients, lacks statistical power, especially for components of composite 1° outcome.
- Contemporary guidelines have based recommendations on the results of multiple subgroup analyses of the SYNTAX trial (including left main stem disease, diabetes, and SYNTAX score), but there was no statistically significant interaction between any of these characteristics and effect of revascularization strategy on outcome.

Heart failure: β -blockers

CIBIS II (Cardiac Insufficiency Bisoprolol Study).

AUTHORS: CIBIS-II Investigators and Committees.

REFERENCE: *Lancet* (1999) 353, 9–13.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Bisoprolol (in addition to conventional medical therapy with ACE inhibition and diuretics) significantly reduces all-cause mortality, CV mortality, and hospitalization in patients with New York Heart Association (NYHA) class III or IV chronic heart failure (CHF).

Impact

β -blockade is now considered standard treatment in contemporary management of CHF; the choice of agent remains controversial.

Aims

Previous small studies and meta-analyses had suggested that β -blockers reduce mortality in patients with CHF. The initial CIBIS trial also suggested such benefits but did not reach statistical significance. CIBIS II was designed to investigate the effects of bisoprolol (a highly selective β_1 adrenoceptor antagonist) on mortality and morbidity in patients with CHF.

Methods

Patients: 2,647 patients from 18 European countries.

Inclusion criteria: CHF NYHA class III or IV:

- Age 18–80y;
- EF $\leq 35\%$;
- Treatment with diuretic and ACE-I (or other vasodilators, if intolerant of ACE-I).

Exclusion criteria:

- Uncontrolled HTN;
- MI or unstable angina in preceding 3mo;
- Percutaneous transluminal coronary angioplasty (PTCA) or CABG in previous 6mo;
- Previous or scheduled cardiac transplantation;
- Atrioventricular block (>1 st degree) without permanent pacemaker;
- Resting heart rate (HR) <60 beats per min or SBP at rest <100 mmHg;
- Serum creatinine >300 micromol/L;
- Reversible obstructive airways disease;
- Pre-existing or planned β -blocker therapy.

Groups:

- Optimal medical therapy and placebo ($n = 1,320$);
- Optimal medical therapy and bisoprolol (1.25–10mg od), titrated according to tolerance ($n = 1,327$).

Primary endpoint: All-cause mortality.

Secondary endpoints:

- All-cause hospital admissions;
- CV mortality;
- CV mortality and CV hospital admissions;
- Permanent premature treatment withdrawals.

Follow-up: Mean F/U 1.3y.

Results

Table 3.18 Summary of results

| Primary endpoint | Placebo | Bisoprolol | HR (95% CI) | p |
|---|-----------|------------|------------------|---------|
| All-cause mortality | 228 (17%) | 156 (12%) | 0.66 (0.54–0.81) | <0.0001 |
| Secondary endpoints | | | | |
| All-cause hospital admissions | 513 (39%) | 440 (33%) | 0.80 (0.71–0.91) | 0.0006 |
| CV mortality | 161 (12%) | 119 (9%) | 0.71 (0.56–0.90) | 0.005 |
| CV mortality and CV hospital admissions | 463 (35%) | 388 (29%) | 0.79 (0.69–0.90) | 0.0004 |
| Permanent premature treatment withdrawals | 192 (15%) | 194 (15%) | 1.00 (0.82–1.22) | 1.0 |

Discussion

This study provided convincing evidence that addition of bisoprolol to standard therapy is beneficial in patients with NYHA classes III and IV CHF. The precise mechanism of benefit was unclear but may include an antiarrhythmic effect interaction with neuroendocrine activation seen in CHF, protection against the toxic effect of catecholamines, and favourable left ventricular (LV) remodelling. To date, metoprolol, bisoprolol, and carvedilol have all been shown to have mortality benefits in the treatment of CHF. The use of β -blockers in severe (NYHA class IV) CHF has been controversial, and such patients were under-represented in CIBIS II and other clinical trials. The COPERNICUS trial (*N Engl J Med* (2001) **344**, 1651–8) addressed this issue and showed that carvedilol was well tolerated and improved survival by 35%, relative to placebo. (See Table 3.18.)

Problems

- Despite proven benefit of β -blockade after MI, the role of these agents in patients with CHF immediately post-MI has been uncertain. The CAPRICORN (*Lancet* (2001) **357**, 1385–90) study confirmed that carvedilol reduced all-cause mortality in patients with recent MI and EF <40%.
- Debate regarding the choice of β -blocker for patients with CHF continues. Carvedilol conferred greater benefit than metoprolol in the COMET trial (*Lancet* (2003) **362**, 7–13), although the long-acting metoprolol preparation previously associated with mortality benefit was not used in this study.

Heart failure: spironolactone

RALES (Randomised **AL**dactone **E**valuation **S**tudy): The effect of spironolactone on morbidity and mortality in patients with severe HF.

AUTHORS: Pitt B, Zannad F, Remme W *et al.*

REFERENCE: *N Engl J Med* (1999) **341**, 709–17.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The addition of spironolactone to standard therapy results in significant mortality and morbidity benefit in patients with severe HF.

Impact

The addition of spironolactone to standard therapy is now recommended practice in the management of severe HF.

Aims

The role of aldosterone in the pathophysiology of HF is well recognized. Its effects are wide-ranging, including salt and water retention, vascular and cardiac fibrosis, and activation of the sympathetic and parasympathetic nervous systems. ACE-Is do not completely inhibit the renin–angiotensin–aldosterone system, and adding an aldosterone receptor blocker may provide incremental benefit. However, co-prescription of these agents can cause hyperkalaemia. This study was designed to assess the efficacy and safety of aldosterone receptor blockade with spironolactone in patients with severe HF already receiving standard therapy (with ACE-I and loop diuretic).

Methods

Patients: 1,663 patients at multiple centres in 15 countries worldwide.

Inclusion criteria: HF diagnosis ≥ 6 wk pre-enrolment:

- NYHA class III or IV HF;
- Treatment with an ACE-I and a loop diuretic;
- EF $\leq 35\%$ within 6mo of enrolment.

Exclusion criteria:

- 1° operable valvular heart disease or congenital heart disease;
- Unstable angina;
- Heart transplantation;
- 1° hepatic failure, active cancer, or any life-threatening disease;
- Serum creatinine > 221 micromol/L or potassium > 5 mmol/L.

Groups:

- Standard therapy and spironolactone (25mg od, uptitrated to 50mg od or downtitrated to 25mg on alternate days, according to symptoms and serum potassium level) ($n = 822$);
- Standard therapy and placebo ($n = 841$).

Primary endpoint: Death from any cause.

Secondary endpoints:

- Death from cardiac causes;
- Hospital admission from cardiac causes;
- Combined incidence of death from, or hospital admission for, cardiac causes.

Follow-up: Mean 24mo.

Results

Table 3.19 Summary of results

| Primary endpoint | Spiro | Placebo | RR (95% CI) | <i>p</i> |
|------------------------------------|-----------|-----------|------------------|-------------------|
| Death | 284 (35%) | 386 (46%) | 0.70 (0.59–0.82) | <0.001 |
| Secondary endpoints | | | | |
| Death from cardiac causes | 226 (27%) | 314 (37%) | 0.69 (0.58–0.82) | <0.001 |
| Hospitalization— cardiac causes | 260/515* | 336/753* | 0.70 (0.59–0.82) | <0.001 |
| Change in NYHA class: | | | | <0.001 |
| Improved | 41% | 33% | | between groups |
| Unchanged | 21% | 18% | | |
| Worsened | 38% | 48% | | |

*Number of events/number of patients.

- The study stopped early when the interim analysis showed spironolactone reduced the overall risk of death by 30% and risk of death attributable to cardiac causes by 31%. This benefit appeared to be due to a lower risk of sudden cardiac death or death from progressive HF.
- Spironolactone was well tolerated. Although statistically significant increases in serum creatinine (4–9micromol/L) and potassium (0.3mmol/L) were seen with spironolactone, these were not considered clinically significant. (See Table 3.19.)

Discussion

Addition of spironolactone to standard therapy in patients with severe HF significantly reduced the risk of death from any cause, death from cardiac causes, combined risk of death and hospital admission for cardiac causes, and deterioration of symptoms, when compared with placebo. The mechanism underlying these beneficial effects remains unclear, but is unlikely to be related to diuresis.

Problems

- Only 10% of patients were taking a β -blocker at the start of the study, although the benefits of spironolactone were not influenced by concurrent β -blockade.
- Gynaecomastia and breast pain were relatively common side effects of spironolactone. Epleronone is a more selective aldosterone receptor antagonist with an improved side effect profile; its benefits have been demonstrated in the EPHESUS trial (*N Engl J Med* (2003) **348**, 1309–21).
- Serious hyperkalaemia was infrequent, possibly because of the relatively low dose of spironolactone and the exclusion of patients with elevated serum creatinine or potassium at baseline. Hyperkalaemia may be more frequent in everyday practice.

Heart failure: angiotensin II receptor antagonists

CHARM (Candesartan in Hear failure Assessment of Reduction in Mortality and Morbidity) trial: Effects of candesartan in patients with CHF and reduced LV systolic function.

AUTHORS: Pfeffer M, Swedburg K, Granger C et al.

REFERENCE: *Lancet* (2003) 362, 759–66.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Fewer all-cause deaths are seen in patients treated with candesartan, in addition to fewer CV deaths or hospital admissions for HF.

Impact

The CHARM programme supports the use of candesartan, irrespective of concurrent treatment or EF in patients with CHF.

Aims

Previous studies had shown ACE-Is, β -blockers, and aldosterone antagonists to reduce mortality and morbidity independently in patients with CHF. Despite these treatments, mortality rates had remained high. The CHARM programme aimed to study the effects of an angiotensin receptor antagonist (candesartan) in patients with CHF, including those previously intolerant of an ACE-I (CHARM Alternative), those already taking an ACE-I (CHARM Added), and those with clinical HF but preserved LV function (CHARM Preserved).

Methods

Patients: 7,601 patients from 618 centres worldwide.

Inclusion criteria:

- NYHA classes II–IV HF of ≥ 4 wk duration;
- Men and women aged ≥ 18 y.

Exclusion criteria:

- Serum creatinine > 265 micromol/L or serum potassium > 5.5 mmol/L;
- Known bilateral renal artery stenosis;
- Symptomatic hypotension;
- Women of childbearing potential not taking adequate contraception;
- Critical aortic or mitral stenosis;
- MI, stroke, open heart surgery in previous 4wk;
- Use of an angiotensin receptor antagonist in previous 2wk.

Component trials: Patients randomized to candesartan or matching placebo in a double-blind fashion, in all three arms:

- CHARM Preserved: LVEF $> 40\%$ ($n = 3,032$);
- CHARM Added: LVEF $\leq 40\%$ and already treated with ACE-I ($n = 2,548$);
- CHARM Alternative: LVEF $\leq 40\%$ and previously intolerant of ACE-I ($n = 2,028$).

Primary endpoint:

- CHARM overall: all-cause mortality;
- CHARM component trials: composite of CV death or hospitalization for CHF.

Secondary endpoints: CV deaths and hospitalization for CHF.

Follow-up: Mean F/U:

- CHARM overall = 37.7mo;
- CHARM Preserved = 36.6mo;
- CHARM Added = 41mo;
- CHARM Alternative = 33.7mo.

Results**Table 3.20** Summary of results

| Primary endpoint | Candesartan (n = 3,803) | Placebo (n = 3,796) | Covariate adjusted HR (95% CI) | p |
|----------------------------|----------------------------|------------------------|-----------------------------------|---------|
| Death any cause | 886 (23%) | 945 (25%) | 0.90 (0.82–0.99) | 0.032 |
| Secondary endpoints | | | | |
| CV death | 691 (18%) | 769 (20%) | 0.87 (0.78–0.96) | 0.006 |
| Hospitalization for HF | 757 (20%) | 918 (24%) | 0.77 (0.70–0.84) | <0.0001 |

Results shown for CHARM overall.

- Similar statistically significant results were seen in CHARM Added and CHARM Alternative, but not in CHARM Preserved. (See Table 3.20.)

Discussion

The theoretical benefit of selective angiotensin II receptor blockade was supported by the results of the programme, demonstrating overall mortality benefit in these high-risk patients with CHF. Candesartan conferred benefit in those already taking current best medical therapy, including an ACE-I, β -blocker, digoxin, loop diuretic, and spironolactone. Component trials showed that the best predictor of mortality was a reduction in LVEF <40% with both arms of CHARM Preserved having significantly better prognosis than the other groups.

CHARM Alternative suggested that candesartan conferred similar benefits to ACE-I and supported the use of candesartan in individuals with CHF who are intolerant of ACE-I. Concerns that excessive renin–angiotensin blockade might be detrimental were not borne out in CHARM Added, which suggested that this practice was safe and reduced CV death and hospitalization for CHF.

Heart failure: implantable cardioverter–defibrillator vs amiodarone

SCD HEFT (Sudden Cardiac Death in HEart Failure Trial): Amiodarone or an implantable cardioverter–defibrillator (ICD) for CCF.

AUTHORS: Bardy G, Lee KL, Mark DB et al.

REFERENCE: *N Engl J Med* (2005) 352, 225–37.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with NYHA class II or III HF and an LVEF of $\leq 35\%$, implantation of a single-lead cardioverter–defibrillator reduces mortality by 23%. Amiodarone has no effect on survival.

Impact

Implantation of a cardioverter–defibrillator should be considered in the management of patients with NYHA class II or III HF and LVEF of $\leq 35\%$.

Aims

Sudden cardiac death is a leading cause of death in patients with HF. Treatment options to prevent sudden death include amiodarone and an ICD. This study was designed to determine whether amiodarone or a single-lead ICD could reduce mortality in patients with mild to moderate HF.

Methods

Patients: 2,521 patients from multiple centres in the USA and Canada.

Inclusion criteria:

- Age >18 y;
- NYHA class II or III chronic stable HF of ischaemic or non-ischaemic aetiology;
- LVEF $\leq 35\%$.

Groups: All patients treated with standard therapies, including ACE-I, β -adrenoceptor blocker, aldosterone receptor blocker, aspirin, and statin, when appropriate:

- Amiodarone: loading dose (800mg od for 1wk), followed by 200mg, 300mg, or 400mg od (depending upon the weight) for 3wk, followed by a maintenance dose of 200–400mg daily ($n = 845$);
- Placebo: double-blinded to identical regime as amiodarone ($n = 847$);
- Single-chamber ICD: implanted a median of 3d after randomization. Shock-only mode—programmed to deliver a shock for ventricular rates of $>187/\text{min}$. Antitachycardia pacing was not permitted, and antibradycardia pacing was only used if the intrinsic HR fell to $<34/\text{min}$ ($n = 829$).

Primary endpoint: All-cause mortality.

Follow-up: Median 45.5mo.

Results

Table 3.21 Summary of results

| | Mortality at 5y | | | | |
|---------------------|----------------------|-------------------------|------------------|------------------------------|-----------------------|
| | Placebo (n = 847) | Amiodarone (n = 845) | ICD (n = 829) | p (amiodarone vs placebo) | p (ICD vs placebo) |
| All patients | 36.1% | 34.0% | 28.9% | 0.5 | 0.007 |
| Ischaemic HF | 43.2% | 41.7% | 35.9% | 0.7 | 0.05 |
| Non-ischaemic HF | 27.9% | 25.8% | 21.4% | 0.7 | 0.06 |
| NYHA class II | 32.0% | 26.4% | 20.1% | 0.2 | <0.001 |
| NYHA class III | 45.6% | 52.8% | 48.4% | 0.01 | 0.3 |

Discussion

This study demonstrated that a single-lead implantable defibrillator reduces the risk of death over 5y by 23% in patients with NYHA class II or III HF and an EF \leq 35%. By contrast, amiodarone did not influence survival. The benefit of ICD therapy was evident in patients with ischaemic and non-ischaemic HF. Unexpectedly, a prespecified subgroup analysis suggested that patients with more severe HF did not benefit from ICD therapy and may be harmed by amiodarone. However, these findings have not been reproduced in other trials. In a subsequent meta-analysis of 12 RCTs, including 8,516 patients with LV systolic dysfunction (*Ann Intern Med* (2007) **147**, 251–62), ICD therapy reduced mortality by 20%. This benefit was mainly driven by a 54% relative reduction in the risk of sudden cardiac death. (See Table 3.21.)

Problems

- Single-chamber ICDs were used; the results cannot be extrapolated to the use of dual-chamber or biventricular devices.
- Over two-thirds of ICD recipients never received a therapeutic ICD shock, and 10% received an inappropriate shock. Further research is required to identify patients most likely to benefit from an ICD.
- The trials of ICD therapy enrolled selected patients; the safety and efficacy of ICD therapy in the wider HF population is unknown.
- Longer-term risks and costs of ICD implantation are also unknown.
- Although ICD therapy improves life expectancy in patients with HF, impact on overall quality of life (QoL) remains controversial.

Heart failure: cardiac resynchronization therapy

CARE-HF (CA**r**D**i**A**c**R**d**i**a**C **RE**S**y**n**c**R**o**n**i**s**a**t**i**o**n****–H**e**a**r**t**F**a**i**l**u**r**e**)** study: The effect of cardiac resynchronization on morbidity and mortality in HF.

AUTHORS: Cleland J, Daubert J, Erdmann E et al.

REFERENCE: *N Engl J Med* (2005) 352, 1539–49.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with NYHA class III or IV HF receiving optimal pharmacological therapy, cardiac resynchronization therapy (CRT) confers additional mortality and morbidity benefit.

Impact

CRT is indicated in patients with NYHA class III or IV HF and evidence of LV dyssynchrony.

Aims

Patients with HF commonly have regions of delayed myocardial activation and contraction, leading to so-called cardiac dyssynchrony. CRT (implantation of an atrio-biventricular pacing system to resynchronize right ventricular and LV activation and contraction) improves symptoms, QoL, and exercise capacity in these patients. This study aimed to assess whether the addition of CRT to standard medical therapy reduced mortality in patients with NYHA class III–IV HF and cardiac dyssynchrony.

Methods

Patients: 813 patients from 82 European centres.

Inclusion criteria: HF diagnosis ≥ 6 wk before enrolment:

- NYHA class III or IV (at time of enrolment);
- EF $\leq 35\%$;
- LV end-diastolic dimension of ≥ 30 mm;
- ECG: QRS complex duration of ≥ 120 ms. If the QRS duration was < 149 ms, two additional echocardiography (echo) criteria for LV dyssynchrony were required.

Exclusion criteria:

- Major CV event in previous 6wk;
- Other indications for pacemaker or implantable defibrillator;
- HF requiring continuous IV therapy;
- Atrial arrhythmias.

Groups:

- Medical therapy alone ($n = 404$);
- Medical therapy and CRT ($n = 409$).

Primary endpoint: Composite of death from any cause or unplanned hospitalization for a major CV event.

Secondary endpoints:

- Death from any cause;
- Composite of death and unplanned hospitalization for HF;
- NYHA and QoL score at 90d;
- Echo assessment of dyssynchrony, LV function, and mitral regurgitation;
- N-terminal pro-brain natriuretic peptide.

Follow-up: Mean 29.4mo.

Results

Table 3.22 Summary of results

| Primary endpoint | Medical alone | Medical + CRT | HR (95% CI) | p |
|--|---------------|---------------|----------------------------|----------|
| Death + hospitalization for major CV event | 224 (55%) | 159 (39%) | 0.63 (0.51–0.77) | <0.001 |
| Secondary endpoints | | | | |
| Death (any cause) | 120 (30%) | 82 (20%) | 0.64 (0.48–0.85) | <0.002 |
| Death or hospitalization (HF) | 191 (47%) | 118 (29%) | 0.54 (0.43–0.68) | <0.001 |
| QoL scores (mean ± SD) | | | Difference (95% CI) | p |
| NYHA class (at 90d) | 2.7 (± 0.9) | 2.1 (± 1.0) | 0.6 (0.4–0.7) | <0.001 |
| Minnesota score | 40 (± 22) | 31 (± 22) | –10 (–8 to –12) | <0.001 |
| EuroQoL EQ-5D | 0.63 (± 0.29) | 0.7 (± 0.28) | 0.08 (0.04–0.12) | <0.001 |

Discussion

This was the first trial to show that CRT alone (without defibrillator capability) improved mortality in patients with HF and LV dyssynchrony. Benefits of CRT were seen in addition to standard medical therapy and irrespective of the aetiology of HF. Use of contemporary medication (ACE-Is, β -blockers, and spironolactone) was high in both groups. (See Table 3.22.)

Problems

- Patients with less severe (NYHA classes I–II) HF have been poorly represented in clinical trials of CRT, and little evidence exists to guide their treatment, even in the presence of LV dyssynchrony. CRT may impact on the natural history of HF, if used earlier in the disease process.
- Identification of patients who benefit most from CRT remains problematic. Patients with QRS prolongation do not necessarily have echo evidence of dyssynchrony and vice versa. New parameters, such as tissue Doppler imaging, are currently being evaluated to optimize patient selection and device programming.

Heart failure: revascularization

STICH TRIAL: Surgical Treatment for Ischaemic Hear Failure.

AUTHORS: Valazques EJ, Lee KL, Marek DA et al.

REFERENCE: *N Engl J Med* (2011) **364**, 1607–16.

STUDY DESIGN: Multicentre, non-blinded RCT.

EVIDENCE LEVEL: 1b.

Key message

Patients with significantly impaired LV function (EF of 35% or less) managed with CABG have no significant difference in all-cause, mortality, compared to patients managed with optimal medical therapy alone. However, patients who undergo CABG have lower rates of CV death and hospitalization from CV causes.

Impact

Routine surgical revascularization for patients with ischaemic cardiomyopathy and poor LV systolic function is no longer supported in the absence of ongoing angina or anatomical CAD, independently supporting CABG.

Aims

Ischaemic cardiomyopathy is the commonest cause of HF in the Western world. Most trials of CABG have excluded patients with significant LV dysfunction, and so benefits of surgery in this group are unknown. This trial was designed to look at the impact of CABG on mortality in this patient cohort.

Methods

Patients: 1,212 patients at 99 sites in 22 countries.

Inclusion criteria:

- Suitable for CABG;
- EF $\leq 35\%$;
- Suitable for medical therapy only if left main stem stenosis $< 50\%$ or angina on treatment with Canadian Cardiovascular Society score < 3 ;
- Suitable for surgical ventricular reconstruction if dominant anterior LV akinesia or dyskinesia.

Groups

- Medical therapy alone ($n = 602$);
- Medical therapy + CABG ($n = 610$).

Follow-up: Median 56mo for 1,207 (99.6%) patients. Minimum 12mo, maximum 100mo.

Primary endpoint: Death from any cause.

Secondary endpoints: Death from a CV cause, death from any cause, or hospitalization for a CV cause.

Results

Table 3.23 Summary of results

| Primary endpoint | Medical | Medical + CABG | p |
|--|-----------|----------------|--------|
| Death from any cause | 244 (41%) | 218 (36%) | 0.12 |
| Secondary endpoints | | | |
| Death from CV cause | 201 (33%) | 168 (28%) | 0.05 |
| Death or hospitalization for any cause | 411 (68%) | 351 (58%) | <0.001 |

Discussion

When compared with medical therapy alone, CABG in patients with suitable anatomy did not alter the 1° outcome of death from any cause. Death rates were higher in patients undergoing CABG for at least the first 2y post-randomization. Although the 2° endpoints seemed to show a difference between the two groups, in terms of death from any cause or hospitalization for any cause, the authors state that this was non-significant, when adjusted for multiple testing. (See Table 3.23.)

Problems

- For obvious reasons, the trial was not blinded, and, although the endpoint adjudication was blinded, non-fatal outcomes may still be subject to bias.
- Caution must be exercised when interpreting 2° outcomes of any clinical trial, if the differences in 1° outcomes of the trial are non-significant.
- The trial has limited statistical power. The death rates were higher in the CABG arm for 2y post-randomization, and longer F/U is required to exclude a late benefit of surgical revascularization.
- The number of patients recruited per site per year is very low.
- Mean age of patient recruited was 59y, not particularly applicable to the majority of real-world patients seen in current cardiological practice who tend to be more elderly.
- Lack of utilization of ICDs or CRT in patients with severe LV dysfunction in the trial is not reflective of contemporary practice, and this may have impacted significantly on the overall outcomes/survival rates/hospitalization in both groups.
- No formal assessment of viability was performed before CABG, and so many patients will potentially have received revascularization to a fully infarcted myocardium, with no expected improvement in function.

Further reading

Jones RH, Velazquez EJ, Michler MD et al. (2009). Coronary bypass surgery with or without surgical ventricular reconstruction. *N Engl J Med* **360**, 1705–17.

Atrial fibrillation: rate vs rhythm control

AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study: A comparison of rate control and rhythm control in patients with atrial fibrillation (AF).

AUTHORS: AFFIRM Investigators.

REFERENCE: *N Engl J Med* (2002) 347, 1825–33.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with AF, a rhythm control strategy to maintain sinus rhythm is associated with a higher risk of adverse drug effects and confers no survival or other advantage over a rate control strategy.

Impact

The majority of patients with AF can be managed safely with a rate control strategy coupled with appropriate anticoagulation. A rhythm control strategy using antiarrhythmic drugs and electrical cardioversion to maintain sinus rhythm may be appropriate for patients at low risk of stroke and recurrent atrial arrhythmia.

Aims

Treatment of AF may be directed towards maintenance of sinus rhythm ('rhythm control') using antiarrhythmic medication and cardioversion. The objective of this strategy is the reduction of symptoms, need for anticoagulation and risk of stroke, and improvement of exercise tolerance and QoL. In the alternative 'rate control' strategy, the ventricular rate can be controlled using drugs that block atrioventricular conduction, coupled with oral anticoagulation to reduce the risk of systemic embolism. This study was designed to compare the long-term effects of these alternative strategies.

Methods

Patients: 4,060 patients from 213 centres in the USA.

Inclusion criteria: AF plus:

- ≥ 65 y of age or other risk factors for stroke;
- AF likely to be recurrent;
- AF likely to cause illness or death;
- Long-term treatment warranted;
- Anticoagulation not contraindicated.

Groups:

- Rate control ($n = 2,027$);
- Rhythm control ($n = 2,033$).

Primary endpoint: All-cause mortality.

Secondary endpoints:

- Composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest;
- Hospitalization;
- Adverse drug reactions.

Follow-up: Median F/U 3.5y (maximum 6y).

Results

Table 3.24 Summary of results

| | Rhythm control | Rate control | <i>p</i> |
|------------------------------|----------------|--------------|----------|
| Death | 26.7% | 25.9% | 0.08 |
| Composite secondary endpoint | 32.7% | 32.2% | 0.3 |
| Hospitalization | 80.1% | 73.0% | <0.001 |
| Adverse drug reaction | 0.8% | 0.2% | 0.007 |

- At 5y, 35% of the rate control group were in sinus rhythm, and over 80% of patients in AF had adequate rate control.
- At each F/U assessment during the trial, ~85% of the rate control group, and 70% of the rhythm control group, were anticoagulated. (See Table 3.24.)

Discussion

In patients with AF and risk factors for stroke, rhythm control offered no advantage over rate control. The rhythm control strategy was associated with a trend towards a higher mortality, but risk of stroke was similar in the two groups. Most strokes occurred in patients in whom anticoagulation had been discontinued or was subtherapeutic, emphasizing the importance of anticoagulation for the prevention of stroke in patients with AF. The rhythm control group had a higher risk of adverse drug effects and admission to hospital.

Problems

- Patients recruited were over 65y of age or had other risk factors for stroke. The results may not be applicable to younger patients without risk factors, including patients with 'lone' AF.
- In AFFIRM, rhythm control did not improve measures of QoL, relative to rate control. The impact of AF on exercise tolerance requires further evaluation.
- Since AFFIRM was reported, there has been considerable interest in surgical and catheter-based procedures to treat AF. These strategies require further evaluation in RCTs.

Dermatology

Introduction 102

Atopic eczema: topical proactive treatment 104

Atopic eczema: systemic treatment with methotrexate vs
azathioprine 106

Psoriasis: photochemotherapy vs dithranol 108

Psoriasis: topical calcipotriol 110

Psoriasis: methotrexate vs ciclosporin 112

Psoriasis: infliximab therapy 114

Psoriasis: ustekinumab therapy 116

Acne: systemic retinoids 118

Bullous pemphigoid: corticosteroids 120

Recurrent cellulitis: treatment 122

Metastatic melanoma: BRAF inhibitors 124

Introduction

Non-dermatologist physicians have long regarded the ability to diagnose and treat skin disease as akin to sorcery, involving the use of long Latin names and an array of bizarre topical concoctions. The enormous number of disease entities encountered by dermatologists gives rise to the paradox that they commonly encounter rarities—for which there is often scant evidence for the treatments used. However, over the past 50y, there have been great advances in our understanding of skin biology and the aetiopathogenesis of skin diseases, and in the development of treatments for these.

With an increased understanding of cutaneous inflammation, there has been widespread development in the use of immunosuppression, either administered directly to the skin or systemically, in the management of common inflammatory skin diseases. Antibiotics and corticosteroids were introduced in the middle of the last century and have had an enormous impact on reducing the morbidity of many skin conditions such as atopic eczema. In addition, immunosuppression with agents, such as azathioprine (AZA), is routinely used for such conditions. The systemic treatment of psoriasis has also been transformed. An evidence-based approach is now used for commonly prescribed topical treatments, phototherapy regimens, and oral systemic immunosuppressants such as methotrexate (MTX) and ciclosporin (CsA). In addition, there are now multiple biological drugs, such as antagonists against tumour necrosis factor (TNF)- α or interleukin (IL)-12/23, that block specific inflammatory pathways central to this disease process. Retinoids have been another major advance; isotretinoin has transformed the management of severe acne vulgaris; the use of acitretin has extended beyond that for psoriasis such as reducing the development of premalignant skin cancers in organ transplant recipients.

An increased understanding of the molecular pathways that are altered in melanoma and the patients' anti-tumour immune response has enabled the development of promising new agents, which have been shown to make a significant improvement in the prognosis of metastatic melanoma. It is anticipated that the development and use of such targeted treatments in all skin cancers will improve outcomes.

Carefully designed studies have been vital in our development of appropriate treatment; however, clinical observation continues to have a role. This was demonstrated by the serendipitous discovery of propranolol as an effective treatment for complicated infantile haemangiomas. The increasing number of therapeutic options for skin conditions does, however, bring the need for better evidence of relative efficacy, acceptability, and long-term safety. This need has been only been fulfilled in part. Moreover, there are still many skin conditions for which limited effective treatments are available such as vitiligo, hidradenitis suppurativa, and viral warts.

This chapter highlights the evidence base for some major advances in dermatology.

Atopic eczema: topical proactive treatment

Efficacy and tolerability of proactive treatment with topical corticosteroids and calcineurin inhibitors for atopic eczema: A systematic review and meta-analysis of RCTs.

AUTHORS: Schmitt J, van Kobyletzki L, Svensson A et al.

REFERENCE: *Br J Dermatol* (2011) **164**, 415–28.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 1a.

Key message

Proactive treatment with topical corticosteroids or calcineurin inhibitors can prevent flares in atopic eczema.

Impact

This approach has significantly altered the management of atopic eczema and possibly prevents the use of systemic oral immunosuppressant therapy. Long-term studies are needed to determine if better management of eczema can prevent allergic sensitization and the 'atopic march' to further atopic disease (food allergy, asthma, allergic rhinitis).

Aims

Atopic eczema is an increasingly common condition, affecting >20% of children. The use of anti-inflammatory topical corticosteroids and calcineurin inhibitors has revolutionized treatment; however, optimal regimens are disputed. Standard topical 'flare' treatment has been the accepted regimen but may only be partly effective. This study aimed to determine the efficacy and tolerability of proactive topical steroids and/or calcineurin inhibitors for flare prevention.

Methods

Inclusion criteria: RCTs reporting on efficacy of topical corticosteroids and/or topical calcineurin inhibitors for flare prevention.

Primary efficacy endpoint: Relapse rate.

Secondary efficacy endpoints:

- Percentage of disease-free days;
- Time to first relapse (days);
- Tolerability.

Results

- All seven double-blind studies, consisting of a treatment stabilization phase, followed by proactive treatment with a vehicle or agent;
- Three, four, and one trial(s) evaluated proactive therapy with topical tacrolimus, fluticasone propionate, and methylprednisolone aceponate, respectively. Each agent was more efficacious in preventing flares than the topical vehicle. Indirect evidence suggests twice weekly application of the potent topical corticosteroid fluticasone propionate is more efficacious than tacrolimus ointment to prevent flares;
- Proactive treatment generally well tolerated. Most frequent tacrolimus side effect (SE)—‘burning’ sensation at application site.

Discussion

In moderate atopic eczema, proactive topical treatment can offer better control and avoid the need for systemic treatments. The effectiveness of proactive treatment is consistent with the knowledge that eczema is a pro-inflammatory state. There is increasing evidence that appropriate control of eczema early in the disease course may reduce flares, allergen sensitization, and the atopic march. Steroid phobia remains a problem, with reluctance to use appropriate topical treatments in certain patients. Topical calcineurin inhibitors may offer an alternative.

Problems

- QoL/effect on atopic march not assessed from the studies.
- Heterogeneity in treatment regimes, outcome measures, choice of 1°/2° outcomes, and definition of ‘flare’.
- Limited generalizability to milder, less frequently relapsing cases commonly encountered in 1° care, as most patients had moderate to severe disease recruited in 2° or tertiary care.
- Need head-to-head trials comparing steroid vs calcineurin inhibitor.
- Need studies to evaluate long-term safety of proactive treatment.

Atopic eczema: systemic treatment with methotrexate vs azathioprine

A randomized trial of methotrexate versus azathioprine for severe atopic eczema.

AUTHORS: Schram ME, Roekevisch E, Leeflang MM *et al.*

REFERENCE: *J Allergy Clin Immunol* (2011) 128, 353–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1a.

Key message

MTX and AZA show comparable short-term efficacy in the treatment of severe atopic eczema.

Impact

Severe atopic eczema is challenging to treat and causes considerable morbidity. Oral systemic immunosuppressants are commonly used; however, few studies have been done to establish their efficacy in this setting. This small, but well-conducted, study demonstrates MTX and AZA to be effective and tolerated therapies. It also illustrates the importance of investigator-led studies where commercial interest is low.

Aims

Severe eczema often requires systemic immunosuppression. CsA is commonly used first-line but is limited by long-term toxicity. MTX and AZA are common second-line agents. This study aimed to compare MTX and AZA in the treatment of severe atopic eczema.

Methods

Patients: 43 adult patients at a single tertiary care centre in the Netherlands.

Inclusion criteria:

- Severe atopic eczema;
- Unresponsive or contraindicated to CsA.

Exclusion criteria:

- Previous treatment with MTX or AZA;
- Pregnant or breastfeeding;
- High alcohol intake;
- If allocated to the AZA group, low/absent thiopurine methyltransferase (TPMT) activity ($<21\text{nmol/g/h}$).

Groups: 1:1 randomization:

- MTX: initiated at 10mg/wk ; escalated to maximum 22.5mg/wk if $<25\%$ improvement at F/U; concomitant folic acid ($n = 20$);
- AZA: initiated at 1.5mg/kg/d ; escalated to maximum 2.5mg/kg/d if $<25\%$ improvement at F/U ($n = 23$).

Primary endpoint: Improvement in severity scoring for atopic eczema (SCORing Atopic Dermatitis, SCORAD) at wk 12.

Secondary endpoints:

- Number of patients achieving $\geq 50\%$ improvement in SCORAD (SCORAD 50);
- Number of patients achieving 'mild' disease;
- Mean change in eczema area and severity index (EASI) and patient-orientated eczema measurement (POEM);
- Mean SCORAD at 24wk.

Results

- Mean SCORAD at 24wk 30.4 in the MTX group, and 33.7 in the AZA group ($p = 0.58$)

Table 4.1 Summary of results

| | Wk 12 | | |
|--|------------|-------------|------|
| | MTX | AZA | p |
| Percentage improvement in SCORAD | 42 (18) | 39 (25) | 0.70 |
| Percentage SCORAD 50 | 40 | 45 | 0.76 |
| Percentage cleared, minimal, or mild disease | 75 | 68.2 | 0.74 |
| Reduction in EASI | 17.4 (6.6) | 17.2 (14.1) | 0.95 |
| Reduction in POEM | 6.9 (5.7) | 7.9 (7.7) | 0.65 |

- No severe/serious adverse events reported, but minor to moderate adverse events common. (See Table 4.1.)

Discussion

This investigator-led study demonstrated similar efficacy of MTX and AZA in severe atopic eczema. Severe atopic eczema can be difficult to treat and causes considerable morbidity. Based on this finding, clinicians can choose a systemic agent, based upon patients' preferences/co-morbidities.

Problems

- Power calculation based on large potential difference in SCORAD. Likely underpowered to detect small differences in 1°/2° outcome measures.
- Set at a single tertiary referral clinic. Systemic treatments for severe eczema also used in 2° care. Reproducibility of findings across multiple centres may be limited.
- High number of adverse events. Safety not an aim of study, but lack of placebo control limits interpretation of adverse events.

Psoriasis: photochemotherapy vs dithranol

Comparison of photochemotherapy and dithranol in the treatment of chronic plaque psoriasis.

AUTHORS: Rogers S, Marks J, Shuster S *et al.*

REFERENCE: *Lancet* (1979) 1, 455–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First RCT to show effectiveness of 8-methoxypsoralen combined with long-wave ultraviolet light (psoralen ultraviolet A, PUVA).

Impact

Photochemotherapy is an effective treatment for moderate to severe psoriasis, but cumulative exposure causes significant increase in skin cancer, which now limits its use.

Aims

Topical dithranol in combination with ultraviolet B (UVB) therapy (Ingram regimen) was a well-established therapy for psoriasis, when psoralen with long-wave ultraviolet light (PUVA) was introduced in the 1970s. This study aimed to compare PUVA with the Ingram regimen for moderate to severe chronic plaque psoriasis.

Methods

Patients: 224 adult patients with moderate to severe psoriasis at two centres (UK).

Inclusion criteria:

- $\geq 10\%$ of body surface area (BSA) involved (excluding the scalp);
- No oral systemic agents in previous month.

Exclusion criteria:

- Pregnant or breastfeeding.

Groups: 1:1 randomization:

- Ingram regimen: daily dithranol at maximal dose tolerated (0.01–0.4%). Removed 24h later, followed by incremental UVB exposure ($n = 111$);
- PUVA regimen: 8-methoxypsoralen (0.6mg/kg) with ultraviolet A (UVA) administered thrice weekly ($n = 113$). UVA starting dose guided by skin type (susceptibility to sunburn).

Follow-up:

- Dithranol: daily evaluation. If no response by 6wk, deemed a therapeutic failure.
- PUVA: three times a week. Up to 30 treatments (10wk) permitted.

Primary endpoint: Psoriasis clearance.

Secondary endpoints:

- Time to clearance;
- SEs of PUVA.

Results

Table 4.2 Summary of results

| Primary endpoint | PUVA | Dithranol with UVB | <i>p</i> |
|----------------------------|--------------|--------------------|----------|
| Psoriasis clearance (%) | 103/113 (91) | 91/111 (82) | <0.05 |
| Mean time to clearance (d) | 34.4 | 20.4 | <0.001 |

- In patients receiving PUVA, 18% developed moderate to severe erythema, which led to treatment withdrawal in two cases. Mild nausea (35%) and pruritus (25%) also reported. (See Table 4.2.)

Discussion

PUVA effectively and rapidly clears chronic plaque psoriasis. Although an important historical study, PUVA is less commonly used today, as it is now known to lead to increased incidence of skin cancer. Narrow-band UVB appears to be safer and is the current standard first-line phototherapy for chronic plaque psoriasis. PUVA is used in resistant cases and a number of other dermatological conditions.

Problems

- Patients' treatment history not given. Patients who previously received multiple alternative topical/systemic treatments may have more resistant disease.
- No follow-up data after initial disease remission. Psoriasis is a chronic disease, and time to relapse is relevant when counselling patients regarding different treatments.

Psoriasis: topical calcipotriol

Systematic review of comparative efficacy and tolerability of calcipotriol in treating chronic plaque psoriasis.

AUTHORS: Ashcroft D, Li Wan Po A, Williams H *et al.*

REFERENCE: *BMJ* (2000) 320, 963–7.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 1a.

Aims

Mild to moderate chronic plaque psoriasis can be effectively managed with a wide range of topical medications. Calcipotriol is a synthetic vitamin D₃ analogue and a popular therapy in both 1° and 2° care. This systematic review aimed to evaluate the comparative efficacy of topical calcipotriol in mild to moderate chronic plaque psoriasis.

Methods

Patients: 6 038 patients with chronic plaque psoriasis reported from 37 trials.

Studies included:

RCTs of 0.005% calcipotriol (cream/ointment) in patients with chronic plaque psoriasis, identified following systematic search (1987–99) of Medline, EMBASE, Cochrane controlled trials register, and BIDS index.

Outcomes:

- Efficacy: mean difference in percentage change in psoriasis area and severity index (PASI) or rate ratio (proportion of patients who achieved ‘marked improvement’ in the calcipotriol group, compared to control);
- Adverse effects: expressed as a rate ratio or NNT.

Results

| Table 4.3 Summary of results | |
|---|-------------------|
| Calcipotriol vs placebo | 44.1% (27.8–60.4) |
| Calcipotriol vs potent topical corticosteroids | 6.5% (2.4–10.6) |
| Calcipotriol vs very potent topical corticosteroids | 10.2% (–0.7–21.1) |
| Calcipotriol vs calcitriol | 50.9% (30.6–71.2) |
| Calcipotriol vs coal tar | 38.9% (26.9–50.9) |
| Calcipotriol vs ‘short-contact’ dithranol | 15.4% (10.1–20.7) |
| Differences in % score on PASI from baseline (selected results only; 95% CI). | |

- Calcipotriol was effective for mild psoriasis, showing superior effect to placebo, calcitriol, coal tar, and short-contact dithranol. No clear difference in efficacy demonstrated between calcipotriol and potent/very potent topical corticosteroids.
- Calcipotriol caused topical irritation; however, dithranol was significantly more irritative than calcipotriol. (See Table 4.3.)

Discussion

Topical calcipotriol had comparable efficacy to potent/very potent topical steroids in chronic plaque psoriasis and was more effective than other commonly used topical preparations. Potent topical steroids had fewer short-term SEs but can lead to skin atrophy, rebound of psoriasis following treatment, and systemic absorption. Current clinical guidelines (National Institute for Health and Care Excellence, NICE, 2012) recommend topical steroids, but calcipotriol as a second-line agent. Emphasis should also be put on patient acceptability and choice.

Problems

Most limitations relate to the 1° studies used in this analysis.

- QoL was assessed in just one of the included studies.
- Many studies used different endpoints to assess treatment efficacy. A standardized approach to reporting disease severity, such as change in PASI or time to skin clearance, would facilitate future meta-analyses.
- Patients often switch between different topical regimens. Trials focusing on combined 'real-world' regimens that include calcipotriol would be informative.

Psoriasis: methotrexate vs ciclosporin

Methotrexate versus ciclosporin in moderate to severe chronic plaque psoriasis.

AUTHORS: Heydendaal V, Spuls P, Opmeer B et al.

REFERENCE: *N Engl J Med* (2003) **349**, 658–65.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There is no significant difference in efficacy between MTX and CsA for the treatment of moderate to severe psoriasis.

Impact

This study established the comparable efficacy of commonly used oral systemic agents for moderate to severe psoriasis, which serves as a benchmark for newer biological agents.

Aims

Systemic agents are often used in refractory and/or widespread psoriasis. These include CsA and MTX. With no consensus as to which was superior, this study aimed to compare MTX and CsA in the treatment of patients with moderate to severe psoriasis.

Methods

Patients: 88 adult patients at one centre (the Netherlands).

Inclusion criteria:

- Moderate to severe chronic plaque psoriasis, as defined by PASI ≥ 8 ;
- Insufficient response to topical/UVB therapy.

Exclusion criteria:

- Previous treatment with MTX or CsA;
- Hepatic/renal impairment;
- Uncontrolled hypertension;
- History of cancer.

Groups: 1:1 randomization:

- MTX: initial dose 15mg/wk; increased to 22.5mg/wk if $<25\%$ improvement at 4wk ($n = 44$).
- CsA: initial dose 3mg/kg/d; increased to 5mg/kg/d if $<25\%$ improvement at 4wk ($n = 44$).

Primary endpoint: Difference in PASI between each group after 16wk of treatment.

Secondary endpoints:

- QoL after 16wk of treatment using Medical Outcomes Study 36-item Short-Form General Health Survey (SF36);
- Reported SEs;
- Long-term efficacy at 1y of treatment;
- QoL at 1y of treatment.

Results

Table 4.4 Summary of results

| Primary endpoint | MTX | CsA |
|-------------------------------|----------------|----------------|
| Baseline PASI (mean \pm SE) | 13.4 \pm 3.6 | 14.0 \pm 6.6 |
| Wk 16 PASI (mean \pm SE) | 5.0 \pm 0.7 | 3.8 \pm 0.5 |

SE, standard error.

- No significant difference in SF36 scores between groups at 16wk;
- Nausea commoner in the MTX group (44% vs 10%; $p < 0.001$); 12 patients in the MTX group discontinued therapy, due to elevated liver enzymes; one patient discontinued CsA due to elevated bilirubin. Biochemical abnormalities normalized on stopping therapy;
- No significant difference in long-term efficacy at 1y between treatments. (See Table 4.4.)

Discussion

This study established comparable efficacy of MTX and CsA in psoriasis; however, in practice, they are often used in different settings. In UK national guidelines (NICE, 2012), MTX is recommended as the first-line oral systemic agent for the long-term management of psoriasis. CsA is recommended for rapid disease control, in palmoplantar pustulosis, and where conception is considered. CsA should not be used continuously for $>1y$ (unless otherwise indicated by a specialist), due to risk of renal toxicity.

Problems

- MTX dosing schedule may not reflect UK practice where dose escalation is often slower.
- The MTX group not given concomitant folic acid. Nausea and elevated liver enzymes associated with folate deficiency. Concomitant folic acid is routine in the UK.

Psoriasis: infliximab therapy

EXPRESS (Evaluation of infliximab for Psoriasis Efficacy and Safety Study): Infliximab induction and maintenance therapy for moderate to severe psoriasis, a phase III, multicentre, double-blind trial.

AUTHORS: Reich K, Nestle F, Papp K *et al.*

REFERENCE: *Lancet* (2005) **366**, 1367–74.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This study has established infliximab as an effective systemic therapy for the treatment of patients with moderate to severe psoriasis.

Impact

The first double-blind RCT to show sustained efficacy of the targeted TNF- α antagonist infliximab in the treatment of psoriasis.

Aims

Biologic therapies that antagonize the pro-inflammatory cytokine TNF- α , such as infliximab, offer effective targeted treatments for psoriasis. This study aimed to assess the efficacy and safety of continuous infliximab therapy in patients with moderate to severe psoriasis.

Methods

Patients: 378 adult patients at 32 dermatology centres (Europe and North America).

Inclusion criteria:

- Moderate to severe chronic plaque psoriasis ≥ 6 mo;
- PASI ≥ 12 , affecting $\geq 10\%$ BSA.

Exclusion criteria:

- History of serious infection;
- Active TB;
- Lymphoproliferative disease.

Groups: 4:1 ratio for infusions of either:

- Infliximab: 5mg/kg at wk 0, 2, and 6, then every 8 wk, up to wk 46 ($n = 301$);
- Placebo \rightarrow infliximab: placebo at wk 0, 2, and 6, then every 8 wk; at wk 24, switched to infliximab treatment as above ($n = 77$).

Primary endpoint: Proportion achieving $\geq 75\%$ improvement in PASI (PASI 75) at wk 10.

Secondary endpoints/measures:

- Proportion achieving PASI 75 at wk 24;
- Proportion achieving physician's global assessment (PGA) score of cleared or minimal at wk 10, 24, and 50;
- Proportion achieving PASI 90;
- Percentage improvement in the nail psoriasis severity index (NAPSI) at wk 10, 24, and 50.

Results**Table 4.5** Summary of results

| | Wk 10 | | | Wk 24 | | | Wk 50 | |
|---------|-------|-----|----------|-------|-----|----------|----------|-----|
| | Plac | Inf | <i>p</i> | Plac | Inf | <i>p</i> | Plac/Inf | Inf |
| PASI 75 | 3% | 80% | <0.0001 | 4% | 82% | <0.0001 | 77% | 61% |
| PASI 90 | 1% | 57% | <0.0001 | 1% | 58% | <0.0001 | 50% | 45% |

Inf, infliximab; Plac, placebo.

- Mean improvement of 26% in NAPSI at wk 10, and 57% improvement at wk 24, which was maintained at wk 50. (See Table 4.5.)

Discussion

These data demonstrated that infliximab monotherapy was highly effective in the treatment of moderate to severe psoriasis. Improvement in skin and nail disease was rapid and sustained in the majority of responders. Treatment was well tolerated, with 80% of patients completing all infusions.

Problems

- Although this study had safety data extending to 1y, concerns remain over the long-term effects of targeted immunosuppression. Drug registries have been created to monitor for potential long-term/rare adverse events.
- A minority of patients that initially responded to infliximab lost this effect (2° failure). Reason for this unclear, but associated with low trough drug levels and development of anti-infliximab antibodies.
- In the UK, the annual drug costs of biologic therapies, such as infliximab, are around £10 000. Traditional oral systemic agents, such as MTX, are much cheaper.

Psoriasis: ustekinumab therapy

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-wk results from a randomized, double-blind, placebo-controlled trial (PHOENIX 1).

AUTHORS: Leonardi C, Kimball A, Papp K *et al.*

REFERENCE: *Lancet* (2008) 371, 1665–74.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Ustekinumab was a safe and effective treatment for patients with moderate to severe psoriasis.

Impact

Landmark phase III, double-blind RCT that demonstrates the efficacy of anti-IL-12/23 biologic therapy for moderate to severe psoriasis. This demonstrates the importance of this pathway in the disease process.

Aims

Most biologic agents licensed for psoriasis target TNF- α . Although efficacious, a significant subset of patients do not respond, or lose their initial response, to such treatments. Ustekinumab targets an alternate pro-inflammatory cytokine pathway (IL-12/23) implicated in psoriasis. The aim of this study was to assess the efficacy and safety of ustekinumab therapy in patients with moderate to severe psoriasis.

Methods

Patients: 766 adult patients at 48 dermatology centres (Europe and North America).

Inclusion criteria:

- Moderate to severe chronic plaque psoriasis for ≥ 6 mo;
- PASI ≥ 12 , affecting $\geq 10\%$ BSA;
- Candidate for systemic or phototherapy.

Exclusion criteria:

- Recent history of serious infection;
- Active TB;
- History of malignancy.

Design: Three-phase study:

- Placebo-controlled phase (wk 0–12);
- Placebo cross-over and active treatment phase (wk 12–40);
- Randomized withdrawal phase (wk 40–76).

Groups: 1:1 randomization:

- Placebo-controlled phase: ustekinumab 45mg ($n = 255$), ustekinumab 90mg ($n = 256$), or placebo ($n = 255$) wk 0 and 4, then every 12wk;
- Placebo cross-over and active treatment phase (wk 12): placebo group allocated to ustekinumab 45mg ($n = 123$) or 90mg ($n = 120$);
- Randomized withdrawal phase (wk 40): ustekinumab groups allocated to continued ustekinumab ($n = 162$) or switched to placebo with reintroduction of ustekinumab if disease relapse ($n = 320$).

Primary endpoint: Proportion achieving $\geq 75\%$ improvement in PASI (PASI 75) at wk 12.

Major secondary endpoints:

- Proportion achieving PGA score of cleared or minimal at wk 12;
- Change in dermatology life quality index (DLQI) at wk 12;
- In randomized withdrawal phase, time to loss of PASI 75 response.

Results

Table 4.6 Summary of results

| | Wk 12 | | Wk 28 | | |
|-------------------------|-------------|-------------|-------------|-------------|-------------|
| | Plac | U'mab 45mg | U'mab 90mg | U'mab 45mg | U'mab 90mg |
| PASI 75 | 3.1% | 67.1% | 66.4% | 71.2% | 78.6% |
| PGA cleared/ minimal | 3.9% | 60.4% | 61.7% | 58.8% | 66.3% |
| Change in DLQI | -0.6 (5.97) | -8.0 (6.87) | -8.7 (6.47) | -8.1 (7.23) | -9.6 (7.56) |

Plac, placebo; U'mab, ustekinumab.

- On treatment withdrawal, the median time to loss of PASI 75 was 15wk; 85% of patients regained PASI 75 response on reintroduction of ustekinumab;
- Serious adverse events rare (similar incidence across all groups, including placebo). (See Table 4.6.)

Discussion

Ustekinumab monotherapy was effective for moderate to severe psoriasis, leading to rapid improvement in disease. Remission was maintained in the vast majority of patients. Ustekinumab offers a 12-weekly SC treatment for psoriasis and is now recommended in UK guidelines (NICE, 2009) as a possible first-line biologic agent. The efficacy of ustekinumab, in addition to TNF antagonists, has increased our understanding of key inflammatory pathways involved in psoriasis.

Problems

- As with other biologic agents used in psoriasis, the long-term safety profile of ustekinumab is not clear. Drug registries monitor for potential long-term/rare adverse events.
- Ustekinumab shares similar cost limitations to other biologic agents, especially in comparison to oral systemic agents.

Acne: systemic retinoids

Isotretinoin versus placebo in the treatment of cystic acne. A randomized double-blind study.

AUTHORS: Peck G, Olsen T, Butkus D et al.

REFERENCE: *J Am Acad Dermatol* (1982) 6, 735–45.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First placebo-controlled RCT to demonstrate the efficacy of oral isotretinoin in the treatment of cystic acne.

Impact

Isotretinoin has revolutionized therapy for patients with severe scarring acne vulgaris. It is efficacious with long-lasting effects observed in the majority of patients.

Aims

Many patients with nodulocystic acne vulgaris do not respond to standard therapy such as oral antibiotics. Isotretinoin, an oral retinoid, treats acne by reducing sebaceous gland sebum production, comedogenesis, and ductal *Propionibacterium acnes* colonization. This was the first placebo-controlled study that investigated the efficacy of oral isotretinoin in nodulocystic acne.

Methods

Patients: 33 patients.

Inclusion criteria:

- ≥ 10 inflamed deep dermal/SC acne cysts or nodules ≥ 4 mm in diameter;
- Minimal response to previous acne therapies;
- No other acne treatment for >1 mo.

Groups: 1:1 randomization:

- Isotretinoin: 0.5mg/kg/d up to 4mo ($n = 16$); increased by 0.5mg/kg/d if no improvement on monthly F/U;
- Placebo: Up to 4mo ($n = 17$). If worsening, cross-over to active drug allowed.

Primary endpoint: Number and size of nodules/cysts.

Secondary endpoints:

- Sebaceous gland size (on skin biopsy);
- Forehead sebum production.

Results

Table 4.7 Summary of results

| | Isotretinoin | Placebo | <i>p</i> |
|------------------------|--------------|---------|----------|
| Change in cysts at 1mo | −17% | +33% | 0.001 |
| Change in cysts at 2mo | −32% | +58% | 0.008 |

- After 2mo, 14 patients taking placebo had switched to isotretinoin, as acne worsened;
- Thirty-two of 33 patients completed at least one 4-mo course of isotretinoin; 27/32 patients reported complete disease clearance at ≥38mo following treatment;
- Reduction in both sebaceous gland size and sebum production. (See Table 4.7.)

Discussion

Oral isotretinoin was highly effective for nodulocystic acne; however, some patients needed >4mo of treatment. No patients stopped treatment due to adverse events, although dose-dependent dryness of mucous membranes was common. Small elevations of liver enzymes and triglycerides were seen but normalized off treatment.

Problems

- This small study was not sufficiently powered to detect important rare adverse events. Isotretinoin prescribing is tightly regulated, due to its teratogenic potential.
- Comparative efficacy against oral antibiotics has not been investigated.
- Alternative treatment regimens for refractory acne, including long-term low-dose isotretinoin, require evaluation.

Bullous pemphigoid: corticosteroids

A comparison of oral and topical corticosteroids in patients with bullous pemphigoid.

AUTHORS: Joly P, Roujeau J, Benichou J et al.

REFERENCE: *N Engl J Med* (2002) **346**, 321–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Topical corticosteroid therapy is effective for bullous pemphigoid (BP), with superior safety to oral corticosteroids in extensive disease.

Impact

Systemic corticosteroids were previously considered standard treatment for BP. This trial has challenged this, suggesting topical corticosteroids be considered first-line.

Aims

Systemic corticosteroids are considered standard treatment for BP, the commonest autoimmune blistering disease of the skin. However, BP is common in the elderly, who often poorly tolerate systemic corticosteroids, and mortality rates are high. This study aimed to assess whether topical corticosteroids effectively controlled BP and improved overall survival.

Methods

Patients: 341 patients at 20 dermatology centres in France.

Inclusion criteria:

- Clinical features of BP;
- Histological findings consistent with BP.

Exclusion criteria:

- Predominant/exclusive mucosal involvement;
- Topical/oral corticosteroids, dapsone, or immunosuppression during previous 6mo.

Groups: 1:1 randomization. Patients stratified by disease severity—‘moderate’ (≤ 10 blisters daily on 3 consecutive days) or ‘extensive’ (> 10 new blisters daily on 3 consecutive days).

- Topical application: 40g/d of 0.05% clobetasol propionate cream for 15d; subsequent reduction over 12mo (moderate $n = 77$; extensive $n = 93$);
- Oral prednisolone: 0.5mg/kg/d for moderate disease or 1mg/kg/d for extensive disease for 15d; subsequent reduction over 12mo (moderate $n = 76$; extensive $n = 95$).

Primary endpoint: Overall survival at 12mo.

Secondary endpoints:

- Disease control at d 21;
- Severe SEs;
- Cumulative hospitalization.

Results

Table 4.8 Summary of results

| Primary endpoint | Topical | Oral | <i>p</i> |
|--|------------------|----------------|----------|
| Survival ^a | | | |
| • Moderate disease | 70% | 70% | 1.0 |
| • Extensive disease | 76% | 59% | 0.02 |
| Secondary endpoints | | | |
| Disease control at d 21 ^a | | | |
| • Moderate disease | 100% (95–100) | 95% (87–99) | 0.06 |
| • Extensive disease | 99% (94–100) | 91% (83–96) | 0.02 |
| Severe SEs | | | |
| • Moderate disease | 32% | 38% | 0.46 |
| • Extensive disease | 29% | 54% | 0.006 |
| Cumulative hospitalization (days) ^a | | | |
| • Moderate disease | 11 (11) | 17 (14) | 0.02 |
| • Extensive disease | 17 (14) | 25 (20) | 0.002 |

^a Mean (95% CI); ^b Mean (± SD).

Discussion

Extensive BP had a poor prognosis, despite treatment with oral prednisolone. Topical corticosteroids were superior in extensive disease. Although survival and disease control were similar in moderate disease groups, cumulative hospital stay was shorter in the topical steroid group. The authors have recommended topical corticosteroids be considered as first-line therapy for patients with both moderate and extensive BP. (See Table 4.8.)

Problems

- Study not blinded. May bias semi-objective 2° endpoints such as blister count or days of hospitalization.
- Small number of patients in each subgroup likely underpowered to draw clear conclusions on 2° endpoints.
- In the UK, patients often managed with corticosteroids and steroid-sparing agents. Thus, most patients do not remain on high-dose systemic steroid regimen, as prescribed in this study. Comparison of 'real-world' regimen with topical corticosteroid therapy alone should be done.

Recurrent cellulitis: treatment

Penicillin to prevent recurrent leg cellulitis.

AUTHORS: Thomas KS, Crook AM, Nunn AJ *et al.*

REFERENCE: *N Engl J Med* (2013) **368**, 1695–703.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Low-dose prophylactic penicillin is effective in reducing the risk of recurrent cellulitis.

Impact

Low-dose penicillin effectively reduced subsequent episodes of recurrent leg cellulitis, without an increase in adverse effects. It should be considered in these high-risk individuals.

Aims

Cellulitis of the leg is a common bacterial infection of the skin and underlying tissues. Current guidelines to prevent recurrent cellulitis are consensus-based, and the use of prophylactic antibiotics is variable among clinicians. The aim of this study was to compare prophylactic low-dose penicillin with placebo for the prevention of recurrent cellulitis.

Methods

Patients: 274 adult patients at 28 centres in the UK.

Inclusion criteria:

- ≥ 2 episodes of leg cellulitis within previous 3y.

Exclusion criteria:

- Use of antibiotics for cellulitis in preceding 6mo;
- Penicillin allergy;
- Previous leg ulceration, surgery, or penetrating trauma.

Groups: 1:1 randomization to 1-y prophylaxis phase, followed by 2-y F/U phase.

- Penicillin 250mg bd for 1y;
- Placebo for 1y.

Primary endpoint: Time to confirmed recurrence of cellulitis.

Secondary endpoints:

- Number of patients with recurrent repeat episodes of cellulitis, or participants with new oedema/ulceration;
- Hospitalized for cellulitis;
- Adverse events;
- Cost-effectiveness.

Results

Median time to first recurrence of cellulitis was increased in the penicillin group (626d vs 532d in the placebo group). (See Table 4.9.).

Table 4.9 Summary of results

| Variable | Recurrence of cellulitis: events/total number of patients (%) | | Percentage point difference (95% CI) | HR (95% CI) | p |
|--------------------------------------|---|-------------|--------------------------------------|------------------|------|
| | Penicillin | Placebo | | | |
| 1° analysis (year 1) | 30/136 (22) | 51/138 (37) | -15 (-26 to -4) | 0.55 (0.35–0.86) | 0.01 |
| 2° analysis: F/U phase years 2 and 3 | 26/97 (27) | 22/81 (27) | 0 (-14 to 12) | 1.08 (0.61–1.93) | 0.78 |

- NNT to prevent one recurrent cellulitis episode was 5 (95% CI 4–9);
- During the F/U period, no significant difference in the rate of cellulitis recurrence;
- The penicillin group had fewer repeat episodes of cellulitis than the placebo group (119 vs 164; $p = 0.02$ for trend);
- No significant difference in adverse events between groups.

Discussion

This large and appropriately powered study demonstrated that penicillin was effective in preventing recurrent cellulitis in patients with a history of leg cellulitis. The protective effect diminished after stopping prophylaxis. The duration of such prophylaxis remains a matter of clinical judgement and may be dependent on the presence of predisposing factors such as chronic lymphoedema.

Problems

- Patients with a high body mass index (BMI), pre-existing oedema, or >3 episodes of cellulitis were less likely to benefit from antibiotic prophylaxis. Such high-risk patients require further investigation to prevent recurrent cellulitis.
- Follow-up data not available for all participants.
- Longer follow-up required to determine if risk reduction can be maintained off prophylaxis.
- The main cause of cellulitis is *Streptococcus A*, for which penicillin resistance is not a current issue. However, it is important to assess the impact of such antibiotic prophylaxis on bacterial resistance.

Metastatic melanoma: BRAF inhibitors

Improved survival with vemurafenib in melanoma with BRAF V600E mutation.

AUTHORS: CHapman P, Hauschild A, Robert C *et al.*

REFERENCE: *N Engl J Med* (2011) **364**, 2507–16.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Vemurafenib improved overall and progression-free survival in patients with BRAF-mutated metastatic melanoma.

Impact

Metastatic melanoma has a poor prognosis. Vemurafenib specifically inhibits the mutated protein kinase BRAF V600E, which is common in melanoma cells. This is the first phase III RCT demonstrating a survival advantage of this targeted therapy.

Aims

Metastatic melanoma has a poor prognosis. Standard treatment with dacarbazine chemotherapy has a poor response rate of just 12%. The majority of melanomas have acquired somatic mutations in the protein kinase BRAF. Vemurafenib specifically inhibits the most commonly mutated BRAF (V600E) genotype. The aim of this trial was to determine if vemurafenib prolongs overall and/or progression-free survival, as compared with dacarbazine.

Methods

Patients: 675 adult patients at 104 centres in 12 countries.

Inclusion criteria:

- Untreated stage IIIC or IV melanoma positive for BRAF V600E mutation;
- Life expectancy ≥ 3 mo;
- Performance status 0 or 1;
- Adequate haematologic, hepatic, and renal function.

Exclusion criteria:

- Additional cancer in previous 5y;
- Progressing/unstable central nervous system (CNS) metastases;
- Concomitant anticancer therapy.

Groups: 1:1 randomization.

- Vemurafenib 960mg bd ($n = 337$);
- Dacarbazine 1 000mg/m² BSA IV infusion 3-weekly ($n = 338$).

Co-primary outcomes: Overall survival and progression-free survival.

Secondary outcomes:

- Response rate and time to response (on computed tomography, CT/magnetic resonance imaging, MRI);
- Adverse events.

Results

Table 4.10 Summary of results

| Primary outcome | Vemurafenib | Dacarbazine | HR (vemurafenib group) |
|--|-------------|-------------|-----------------------------------|
| Mean overall survival at 6mo ($n = 672$) | 84% (78–89) | 64% (56–73) | 0.37 (0.26–0.55; $p < 0.001$) |
| Median progression-free survival ($n = 549$) | 5.3mo | 1.6mo | 0.26 (0.20–0.33; $p < 0.001$) |
| Response rate | 48% (42–55) | 5% (3–9) | |
| Median time to response | 1.45mo | 2.7mo | |

Values in brackets are 95% CI.

- Common adverse events in the vemurafenib group: rash, arthralgia, and fatigue; 18% developed cutaneous squamous cell carcinoma (SCC) and/or keratoacanthoma (KA);
- Common adverse events in the dacarbazine group: fatigue, nausea, vomiting, and neutropenia. (See Table 4.10.)

Discussion

Vemurafenib was associated with a significant reduction in death and tumour progression in patients with metastatic melanoma. At interim analysis (118 patient deaths), patients in the dacarbazine group were allowed to cross-over to receive vemurafenib. Vemurafenib and the additional new agents that enhance anti-tumour immune responses offer new treatment options for patients with metastatic melanoma.

Problems

- Response rate to dacarbazine lower than in other trials. BRAF-mutated melanomas may be more aggressive than, or less sensitive to, dacarbazine.
- Cutaneous SCC and KA in the vemurafenib group. Mechanism underlying their development and effect on prognosis must be evaluated.
- Sponsor involved in the study design, data collection, and analysis—
influence unclear.

Diabetes

Introduction 128

T1DM: insulin pump therapy vs multiple daily insulin injections 130

T1DM: islet cell transplantation 132

T2DM: intensive glucose control 134

T2DM: intensive glucose lowering 136

T2DM: intensive blood pressure control 138

T2DM: bariatric surgery and cardiovascular risk 140

T2DM: GLP-1 analogues 142

T2DM: benefits of calorie restriction 144

T2DM: multiple risk factor intervention 146

Introduction

In the UK general population, ~1 in 20 people has diabetes, and, in hospital-based patients, the prevalence is ~1 in four. We are experiencing an epidemic of obesity-driven T2DM, and it is expected that this will be followed by a wave of CV disease and diabetes-related complications.

The past few years have given us several important studies that have guided physicians regarding the most appropriate medical and surgical therapies for patients with diabetes. The focus of many of these studies has been the prevention of CV disease, because this is the main cause of death and disability in this group of patients.

It can be difficult for physicians to find time to update themselves on the key pieces of evidence underpinning the practice of diabetes medicine. This chapter focuses on the clinical trials and evidence that has had the greatest impact on the treatment of diabetes over the past few years.



T1DM: insulin pump therapy vs multiple daily insulin injections

Comparison of the effects of continuous subcutaneous insulin infusion (CSII) and NPH-based multiple daily insulin injections (MDI) on glycaemic control and quality of life: results of the 5-nations trial.

AUTHORS: Hoogma R, Hammond P, Gomis R et al. (5-Nations Study Group).

REFERENCE: *Diabet Med* (2006) 23, 141–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Largest RCT to first show the benefits of continuous subcutaneous insulin infusion (CSII) over multiple daily injections (MDIs) in people with type 1 diabetes (T1DM).

Impact

This trial demonstrated the benefits of CSII over an MDI regime based on rapid-acting insulin analogues and Neutral Protamine Hagedorn (NPH) insulin, including improved glycaemic control, reduced blood glucose fluctuations, and less hypoglycaemia. There was also improved treatment satisfaction, QoL, mental health, and flexibility with eating and lifestyle.

Aims

Prior to this trial, studies comparing CSII with MDI had been limited, because of inadequate design, small sample sizes, or the use of outdated insulin or pump technology. The authors sought to compare CSII with MDI, with respect to glucose levels assessed by HbA1c, glucose fluctuation, hypoglycaemia, and QoL in an adequately powered RCT with a cross-over design.

Methods

Patients: 272 patients at 11 centres in five European countries.

Inclusion criteria:

- Age 18–65y, with T1DM (C-peptide negative);
- On MDI for at least 6mo;
- Ability to manage intensive therapy (frequent blood glucose testing, carbohydrate counting, insulin dose adjustment, CSII use).

Exclusion criteria:

- Hypoglycaemic unawareness;
- Progressive retinopathy;
- Creatinine >250micromol/L;
- Recent ACS or stroke;
- Uncontrolled HTN;
- Autonomic neuropathy;
- Planned or existing pregnancy.

Groups: 2-mo run-in, followed by cross-over design involving 2×6 -mo treatment period, with identical blood glucose targets for each of the MDI and CSII groups.

Primary outcome measure: HbA_{1c} at end of each treatment period.

Main secondary outcome measures: Daily blood glucose fluctuation (defined as average SD of mean daily blood glucose during the 14d prior to the final visit for each treatment period), hypoglycaemia, QoL.

Follow-up: 16-mo total treatment period.

Results

- End-of-trial HbA_{1c} was significantly lower in the CSII group (7.45%), compared with the MDI group (7.67%) ($p < 0.001$);
- Glucose fluctuations (blood glucose SD) lower on CSII, compared with MDI (3.9mmol/L vs 4.3mmol/L) ($p < 0.001$);
- CSII use associated with fewer episodes of mild hypoglycaemia (49.3 vs 55.4 events per patient) and severe hypoglycaemia (0.2 events per patient vs 0.5 events per patient), compared with MDI;
- QoL ($p < 0.001$), treatment satisfaction, diabetes-related worry, and flexibility with regard to lifestyle ($p < 0.05$) were all better with CSII, compared with MDI;
- A higher proportion said that they would recommend CSII to someone with diabetes, compared with MDI;
- CSII was associated with a small number of infusion site problems—skin reactions and local pain (0.19 events per patient per year).

Discussion

The trial demonstrated the superiority of CSII over an NPH-based MDI regimen, with respect to HbA_{1c} , reduced mean blood glucose levels and blood glucose fluctuations, and a reduction in the incidence of severe and mild episodes of hypoglycaemia. The dual benefit of CSII over MDI (better glucose control and fewer hypoglycaemic episodes) goes beyond the results of the Diabetes Control and Complications Trial, in which intensified treatment was associated with a 3-fold increased risk of hypoglycaemia, compared with the usual care.

Problems

- NPH insulin, instead of insulin glargine or detemir, which are more commonly used today;
- Researchers were not blinded to the intervention.

Further reading

National Institute for Health and Care Excellence (2008). *Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus*. Available at: <http://www.nice.org.uk/nicemedia/pdf/ta151guidance.pdf>.

Yeh HC, Brown TT, Maruthur N et al. (2012). Comparative effectiveness and safety of methods of insulin delivery and glucose monitoring for diabetes mellitus: a systematic review and meta-analysis. *Ann Intern Med* 157, 336–47.

T1DM: islet cell transplantation

Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppression regimen.

AUTHORS: Shapiro A, Lakey J, Ryan E et al.

REFERENCE: *N Engl J Med* (2000) 343, 230–8.

STUDY DESIGN: Cohort study.

EVIDENCE LEVEL: 2b.

Key message

Islet transplantation in carefully selected people with T1DM can achieve freedom from exogenous insulin and provide glycaemic control and stability.

Impact

This landmark study showed that patients with T1DM and a history of severe potentially life-threatening hypoglycaemia could be successfully treated by islet cell transplantation, using an immunosuppressive regime that avoided steroids. This paper favourably influenced worldwide opinion regarding this treatment modality.

Aims

Prior to this report, patient outcomes following islet cell transplantation were poor. Previously, most procedures had been performed in combination with kidney transplantation and using immunosuppression regimes that consisted of antibody induction with an antilymphocyte globulin combined with ciclosporin, AZA, and glucocorticoids. This study reported outcomes in patients with severe hypoglycaemia without renal impairment, treated with a steroid-free immunosuppression regime.

Methods

Patients: Seven patients at a single centre in Canada.

Inclusion criteria

- T1DM (C-peptide negative);
- Recurrent severe hypoglycaemia or metabolic instability;
- Estimated risks of diabetes instability exceeded that of transplantation.

Exclusion criteria: Renal impairment.

Design:

- 1-y prospective cohort study;
- Immunosuppression: sirolimus, tacrolimus, daclizumab (no steroids).
- Each patient received two or three transplants (each >4,000 islet equivalents per kg of the recipient's body weight).

Primary outcome measures:

- Insulin independence and C-peptide positivity;
- Mean amplitude of glucose excursions (average difference between high and low blood glucose readings);
- Oral glucose tolerance and mixed meal testing;
- HbA_{1c}.

Results

- All patients became free of exogenous insulin injections and were C-peptide-positive;
- The mean amplitude of glycaemic excursions was significantly decreased after the attainment of insulin independence, from 11.1 ± 1.8 mmol/L before transplantation to 2.8 ± 1.7 mmol/L after the attainment of insulin independence; $p < 0.001$;
- Oral glucose tolerance normalized in all recipients;
- HbA_{1c} values were normal after transplantation in all recipients;
- There were no further episodes of hypoglycaemic coma;
- Complications were minor.

Discussion

This landmark paper changed opinion worldwide regarding the potential success of islet cell transplantation. The researchers transplanted an adequate number of viable, well-characterized islets which had been prepared without contact with animal proteins and with the minimum duration of cold ischaemia. The novel immunosuppression regime that avoided steroids was considered to be an important component of the success of this protocol. Islet cell transplantation was shown to be effective and safe and has since been considered a viable alternative to the more invasive procedure of whole-organ pancreas transplantation.

Limitations

- There was no control group, and F/U was limited to 1y, so too short to evaluate 2° diabetic complications;
- The psychological risks and benefits of the procedure were not documented;
- Unclear which component of the 'Edmonton protocol' was responsible for the improved outcomes, compared with previous therapies.

Further reading

de Kort H, de Koning EJ, Rabelink TJ et al. (2011). Islet transplantation in type 1 diabetes. *BMJ* 342, d217.

Diabetes UK. *Islet transplants*. <https://www.diabetes.org.uk/Guide-to-diabetes/What-is-diabetes/Diabetes-treatments/#islets>.

T2DM: intensive glucose control

UKPDS (UK Prospective Diabetes Study) follow-up: 10-y follow-up of intensive glucose control in T2DM.

AUTHORS: Holman R, Paul S, Bethel M *et al.*

REFERENCE: *N Engl J Med* (2008) **359**, 1577–89.

STUDY DESIGN: RCT (post-trial monitoring).

EVIDENCE LEVEL: 1b.

Key message

Improve glucose control in the UKPDS produced important long-term benefits on mortality, and macrovascular and microvascular complications, even though between-group differences in glucose levels were lost 1y after the end of the trial.

Impact

Glucose-lowering using sulfonylurea therapy, insulin, or metformin yielded important clinical benefits that persisted beyond the end of the trial. This led to the concept of 'glycaemic memory', meaning that prior glycaemic control can have lasting clinical benefits.

Aims

Prior to this report, it was unclear whether improved glycaemic control would have any long-term clinical benefits. The UKPDS researchers performed post-trial monitoring to determine whether this improved glucose control persisted and whether such therapy had a long-term effect on mortality and diabetes-related complications.

Methods

Patients: 3,277 of the original 5,102 UKPDS patients available for post-trial monitoring.

Inclusion criteria: Age 25–65y at baseline, with newly diagnosed T2DM.

Exclusion criteria:

- Serum creatinine >175micromol/L;
- MI in the previous year;
- HF, angina, or >1 major vascular event;
- Retinopathy requiring laser therapy;
- Malignant HTN.

Groups:

- Prior intensive therapy with sulfonylurea or insulin ($n = 2,729$);
- Prior intensive therapy with metformin in overweight patients ($n = 342$);
- Prior conventional therapy with diet ($n = 1,138$).

Main outcome measures:

- Any diabetes-related endpoint;
- Diabetes-related death, death from any cause;
- MI, stroke, peripheral vascular disease;
- Microvascular disease (vitreous haemorrhage, retinal photocoagulation, or renal failure).

Follow-up: A 10-y follow-up study performed after the end of the original trial. No attempt made to maintain previously randomized therapies. Patients seen annually for 5y in UKPDS clinics, then F/U by questionnaire. Clinical examinations performed every 3y.

Results

- Between-group differences in glucose levels were lost after the first year;
- In the sulfonylurea–insulin group, relative reductions in risk persisted at 10y for:
 - Any diabetes-related endpoint (9%, $p = 0.04$);
 - Microvascular disease (24%, $p = 0.001$);
 - MI (15%, $p = 0.01$);
 - Death from any cause (13%, $p = 0.007$);
- In the metformin group, significant risk reduction in overweight patients persisted for:
 - Any diabetes-related endpoint (21%, $p = 0.01$);
 - MI (33%, $p = 0.005$);
 - Death from any cause (27%, $p = 0.002$).

Discussion

Clinical benefits of prior glucose-lowering persisted, despite the early loss of within-trial differences in glucose levels. Insulin or sulfonylurea therapy was associated with statistically significant reductions in the risk for MI and death from any cause in this post-trial observation period (but not in the original trial). Reduced risk of mortality through glucose-lowering contrasts with the results of the more recent Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, which showed that a strategy to normalize glucose levels led to an increase in mortality (*N Engl J Med* (2008) **358**, 2545–59). The differences in trial results may be explained by differences in age, state of diabetes, and hypoglycaemia.

Limitations

- Questionnaires (years 6–10) may not have captured all the non-fatal outcomes;
- Biochemical and clinical measurements were not collected after the fifth year of F/U.

Further reading

Rutter MK, Nesto RW (2011). Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care. *Eur Heart J* **32**, 2247–55.

T2DM: intensive glucose lowering

Effects of intensive glucose lowering in type 2 diabetes.

AUTHORS: Gerstein H, Miller M, Byington R et al. (Action to Control Cardiovascular Risk in Diabetes Study Group).

REFERENCE: *N Engl J Med* (2008) **358**, 2545–59.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Attempts to normalize blood glucose levels led to increased mortality and did not significantly reduce major CV events.

Impact

The trial identified previously unrecognized harm through intensive lipid-lowering in high-risk patients with T2DM. This has led to guidelines recommending personalized (and not generalized) blood glucose targets for patients with T2DM.

Aims

Prior to this trial, the CV effects of normalizing blood glucose in patients with T2DM were unknown. The study investigated whether intensive therapy and normalizing blood glucose levels would reduce CV events in patients with T2DM who had either established CV disease or additional CV risk factors.

Methods

Patients: 10,251 patients at 77 centres across the USA and Canada.

Inclusion criteria:

- Age 40–79y with T2DM and established CV disease; or
- Age 55–79y with T2DM with evidence of atherosclerosis, albuminuria, LV hypertrophy, or at least two additional risk factors for CV disease.

Exclusion criteria:

- Frequent or recent serious hypoglycaemia;
- Unwilling to do home glucose monitoring or inject insulin;
- BMI >45kg/m²;
- Serum creatinine >133micromol/L;
- Other serious illness.

Groups: 2 × 2 factorial design, with 4,733 patients assigned to lower their BP by intensive therapy (systolic target <120mmHg) or standard therapy (target <140mmHg), and 5,518 patients assigned to receive either fenofibrate or placebo with simvastatin:

- Intensive therapy (*n* = 5,128): target HbA_{1c} <6.0%;
- Standard therapy (*n* = 5,123): target HbA_{1c} <7.0–7.9%.

Primary outcome: CV death or non-fatal MI or stroke.

Follow-up: 3.5y (trial terminated early due to safety concerns).

Results

- Higher mortality in intensively vs standard-treated patients led to early termination of the trial (5% vs 4%, HR 1.22, 95% CI 1.01–1.46, $p = 0.04$);
- HbA_{1c} levels were 6.4% with intensive therapy and 7.5% with standard therapy;
- During 3.5y of follow-up, mortality risk was higher in intensively treated patients, compared with the standard therapy group (HR 1.22, 95% CI 1.01–1.46, $p = 0.04$);
- During the follow-up period, the 1° outcome was not significantly lower in intensively treated patients, compared to the standard therapy group (HR 0.90, 95% CI 0.78–1.04, $p = 0.16$).

Discussion

The higher mortality in intensively treated patients was a great surprise to many physicians in the diabetes community. The absolute risk of death was increased by 1%, which is equivalent to one extra death for every 95 patients treated for 3.5y. The cause of the increased mortality was uncertain. Possible explanations include: hypoglycaemia, weight gain, and the effect of individual drugs or drug combinations.

Problems

- The study was not able to assess the cause of the higher mortality in the intensively treated patients.

Further reading

Rutter MK, Nesto RW (2011). Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care. *Eur Heart J* 32, 2247–55.

T2DM: intensive blood pressure control

ACCORD (Action to Control Cardiovascular Risk in Diabetes) blood pressure (BP) study: Effects of intensive BP control in T2DM.

AUTHORS: ACCORD Study Group, Cushman W, Evans G, Byington R et al.

REFERENCE: *N Engl J Med* (2010) 362, 1575–85.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Attempts to normalize BP, targeting an SBP of <120mmHg, did not reduce the risk for major CV events, when compared to targeting <140mmHg.

Impact

This study has led to physicians avoiding attempts to 'normalize' BP in patients with T2DM.

Aims

Prior to this trial, the CV benefits of normalizing BP in patients with T2DM were unknown. This non-blinded study aimed to test the effect of a target SBP of <120mmHg on major CV events, when compared to a strategy targeting an SBP of <140mmHg, using medications available in clinical practice at the time of the trial that were known to reduce CV disease risk in T2DM.

Methods

Patients: 4,733 patients from several centres across the USA and Canada, taking part in the 1° ACCORD study.

Inclusion criteria:

- Age 40–79y with T2DM and established CV disease, or age 55–79y with T2DM and evidence of atherosclerosis, albuminuria, LV hypertrophy, or at least two additional risk factors for CV disease;
- SBP 130–180mmHg and taking ≤ 3 antihypertensive medications;
- Urine protein <1g/d.

Exclusion criteria:

- BMI >45kg/m²;
- Serum creatinine >133micromol/L;
- Other serious illness.

Groups: Physicians free to choose the type of medication used:

- Intensive therapy ($n = 2,362$): target SBP <120mmHg;
- Standard therapy ($n = 2,371$): target SBP <140mmHg.

Primary outcome: CV disease death, non-fatal MI, or stroke.

Follow-up: For 5y. Symptom checklist administered at baseline, and at 1, 3, and 4y. Intensive group: 1×/month for 4mo, then every 2mo. Standard group: months 1 and 4, then every 4mo.

Results

- SBP 14mmHg lower in intensively treated patients: 119mmHg (95% CI 119–120) vs 134mmHg (95% CI 133–134);
- Hypotension (0.7% vs 0.04%, $p > 0.01$), arrhythmia (0.5% vs 0.13%, $p = 0.02$), hyperkalaemia (0.4% vs 0.04%, $p = 0.01$), and the development of renal impairment (estimated glomerular filtration rate (eGFR) $< 30\text{mL}/\text{min}/1.73\text{ m}^2$: 4.2% vs 2.2%, $p = 0.12$) were commoner in intensively treated patients;
- No significant difference in the risk for the 1° outcome (1.9% per year in the intensive therapy group vs 2.1% in the standard therapy group; HR (95% CI) 0.88 (0.73–1.06), $p = 0.20$);
- Total mortality and CV disease mortality rates did not differ in the therapy groups ($p = 0.55$ and 0.74 , respectively);
- The risk of stroke was lower in intensively treated patients (HR (95% CI) 0.53 (0.39–0.89), $p = 0.01$).

Discussion

Normalizing BP levels in these patients did not reduce overall CV disease risk and led to an increased risk of adverse events, including renal impairment. The NNT to prevent one stroke over 5y was calculated to be 89. Target BP levels in this trial were much lower than in previous studies (see Further reading), and this may explain the discrepancy in results. The ‘ideal’ target SBP may be ~130mmHg (midway between the two targets in this trial). There may be a J-shaped relationship between BP and CV disease risk.

Limitations

- The CV event rate was 50% lower than the expected rate, perhaps due to high use of statin medication and the fact that patients with hyperlipidaemia were recruited into ACCORD with the trial.

Further reading

Rutter MK, Nesto RW (2011). Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care. *Eur Heart J* 32, 2247–55.

T2DM: bariatric surgery and cardiovascular risk

SOS (Swedish Obese Subjects) study: CV events after bariatric surgery in obese subjects with T2DM.

AUTHORS: Romeo S, Maglio C, Burza M et al.

REFERENCE: *Diabetes Care* (2012) **35**, 2613–17.

STUDY DESIGN: Case control.

EVIDENCE LEVEL: 3b.

Key message

Bariatric surgery reduces the incidence of MI in obese individuals with T2DM.

Impact

The study provides the first good-quality evidence that bariatric surgery has CV benefits in patients with T2DM.

Aims

The CV benefits of bariatric surgery in patients with T2DM were unknown prior to this study. This carefully conducted case control study aimed to assess the CV impact of bariatric surgery over a long (13-y) follow-up period.

Methods

Patients: 607 patients.

Inclusion criteria:

- Age 37–60y with T2DM;
- BMI $\geq 34\text{kg/m}^2$ for men and $\geq 38\text{kg/m}^2$ for women.

Exclusion criteria:

- Prior bariatric surgery or surgery for gastric or duodenal ulcer;
- Gastric ulcer within the preceding 6mo;
- Malignancy during the previous 5y;
- MI within the preceding 6mo;
- Eating disorder, drug or alcohol abuse, psychiatric or other psychological problems.

Design:

- Patients were matched for 18 clinical variables;
- All participants had regular follow-up.

Treatment groups:

- Surgery ($n = 345$): the surgical procedures were: $n = 227$ —vertical-banded gastropasty; $n = 61$ —gastric banding; and $n = 57$ —gastric bypass medication;
- Control ($n = 262$): subjects received local standard medical obesity and diabetes therapies.

Primary outcome:

- Fatal and non-fatal CV events (MI and stroke), analysed separately and together.

Follow-up: 13y.

Results

- Follow-up was 79–89% at 2y;
- The surgery group had higher baseline BMI, BP, and total cholesterol, when compared with the control group;
- Bariatric surgery was associated with significant improvements in body weight, blood glucose, lipids, and BP ($p < 0.001$ for all), compared with controls;
- Fewer first-time CV events occurred in the surgical group (63 events in 345 patients vs 65 events in 262 controls; unadjusted HR 0.63 [95% CI 0.45–0.90], $p = 0.010$);
- Surgery was associated with a lower risk of MI (HR 0.59 [95% CI 0.38–0.92], $p = 0.018$), but similar rates of stroke (HR 0.95 [95% CI 0.56–1.61], $p = 0.85$);
- Total of 16 patients with T2DM would need to be treated by bariatric surgery to prevent one MI over 15y.

Discussion

In the general population, bariatric surgery had been shown to have a modest effect on the risk of subsequent CV events. The benefits of surgery appeared greatest in those with dyslipidaemia and fasting insulin, suggesting that metabolic parameters might help to select these patients for surgery.

Limitations

- This was not a randomized intervention;
- It was a post hoc analysis, selecting only individuals with T2DM of baseline.

Further reading

Sjöström L, Peltonen M, Jacobson P et al. (2012). Bariatric surgery and long-term cardiovascular events. *JAMA* 307, 56–65.

T2DM: GLP-1 analogues

LEAD-6 (Liraglutide vs exenatide for type 2 diabetes) study: Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial.

AUTHORS: Buse J, Rosenstock J, Sesti G et al. (LEAD-6 Study Group).

REFERENCE: *Lancet* (2009) **374**, 39–47.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Liraglutide once a day provided significantly greater improvements in glycaemic control than exenatide twice a day, and was generally better tolerated.

Impact

The results suggested that liraglutide might be a particularly suitable treatment option, when weight loss and risk of hypoglycaemia are major considerations.

Aims

Glucagon-like peptide-1 (GLP-1) receptor agonists had been established as effective glucose-lowering drugs that promoted weight loss in patients with T2DM. This study aimed to compare the efficacy and safety of liraglutide, a human GLP-1 analogue, with exenatide, an exendin-based GLP-1 receptor agonist.

Methods

Patients: 464 patients from centres in 15 countries.

Inclusion criteria:

- Age 18–80y with T2DM;
- Poor glucose control (HbA_{1c} 7–11%) on maximum metformin, sulfonylurea, or both;
- $\text{BMI} \leq 45 \text{ kg/m}^2$.

Exclusion criteria:

- Prior long-term insulin therapy;
- Prior exposure to liraglutide or exenatide;
- Impaired liver or kidney function, or significant CV disease;
- Retinopathy or maculopathy requiring acute treatment;
- $\text{BP} \geq 180/100 \text{ mmHg}$.

Groups: Stratified by previous oral antidiabetic therapy. After an initial dose escalation period, the dose of each drug was fixed, and intolerance to these doses required study discontinuation:

- Liraglutide 1.8mg od ($n = 233$);
- Exenatide 10 micrograms bd ($n = 231$);

Primary outcome: Change in glucose control, assessed by HbA_{1c}.

Follow-up: 26wk.

Results

- Glucose lowering greater with liraglutide than exenatide: estimated treatment difference -0.33% (95% CI -0.47 to -0.18);
- Proportion of participants achieving an HbA_{1c} target of $<7\%$ higher with liraglutide than exenatide (54% vs 43%; OR 2.0; 95% CI 1.3–3.1);
- No difference in weight loss: liraglutide -3.2kg vs exenatide -2.9kg ; difference: 0.4kg (95% CI -1.0 to 0.2 , $p = 0.2235$);
- Serious adverse events commoner with liraglutide than with exenatide (5.1% vs 2.6%). Commonest SE was nausea, which was lower at 6wk with liraglutide, compared with exenatide;
- Number of episodes of severe hypoglycaemia was too small to analyse statistically, but the proportion of patients with minor hypoglycaemia was lower with liraglutide than exenatide (1.9 vs 2.6 events per patient per year, $p = 0.01$).

Discussion

Liraglutide was superior to exenatide with regard to glucose lowering and the risk of hypoglycaemia. These results suggest that liraglutide might be a treatment option for patients with T2DM, particularly when weight loss and the risk of hypoglycaemia are major considerations.

Limitations

- This was an open-label intervention;
- Largely white ethnic group;
- The study was underpowered to assess the risk of rare SEs.

Further reading

Russell-Jones D, Vaag A, Schmitz O *et al.*; LEAD-5 Study Group (2009). Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial. *Diabetologia* 52, 2046–55.

T2DM: benefits of calorie restriction

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol.

AUTHORS: Lim E, Hollingsworth K, Aribisala B et al.

REFERENCE: *Diabetologia* (2011) 54, 2506–14.

STUDY DESIGN: Case control.

EVIDENCE LEVEL: 3.

Key message

Dietary energy restriction resulted in normalization of insulin secretion and hepatic insulin sensitivity in patients with T2DM.

Impact

Results of the study showed that the underlying abnormalities in insulin secretion and response in some patients with T2DM could be reversed through lifestyle intervention, giving hope to many patients.

Aims

Prior to this study, T2DM was considered a chronic progressive condition that could be partially treated, but not cured. The study aimed to assess whether a sudden negative energy balance could reduce pancreatic and liver fat, and reverse T2DM by improving insulin secretion and insulin resistance.

Methods

Patients

- A total of 14 patients with T2DM (nine completed the intervention);
- A total of 9 control participants with normal glucose tolerance matched for weight, age, and sex.

Inclusion criteria (T2DM group):

- Age 35–65y with T2DM;
- HbA_{1c} 6.5–9.0%;
- Diabetes duration <4y.

Exclusion criteria:

- Prior therapy with thiazolidenediones, insulin, steroids, or β -blocker;
- Serum creatinine >150micromol/L; liver transaminase >2.5-fold above the reference range;
- Contraindications for magnetic resonance scanning.

Intervention:

- The intervention consisted of a 2.5MJ (600kcal)/d liquid diet formula (510kcal/d plus three portions of non-starchy vegetables);
- There was no dietary intervention in control participants.

Primary outcome: Change in glucose control, assessed by HbA_{1c}.

Follow-up: β -cell function, insulin sensitivity, and liver and pancreatic fat were assessed at baseline and after 1, 4, and 8wk of a low-calorie diet in patients with diabetes. Control participants were studied on one occasion only.

Results

- Average weight loss during 8wk was 15.3kg (15% of initial body weight);
- After 1wk, fasting plasma glucose normalized in the diabetic group (from 9.2 to 5.9mmol/L, $p = 0.003$);
- Liver insulin sensitivity (rose from 42 to 74, $p = 0.003$) and triacylglycerol content (fell from 12.8 to 2.9, $p = 0.003$) improved, compared with the control;
- The first-phase insulin response increased (from 0.19 to 0.46, $p < 0.001$), compared with controls, and approached control values, as pancreatic triacylglycerol was reduced;
- Maximal insulin response became supranormal at 8wk (1.37 treatment vs 1.15 controls).

Discussion

This study showed, for the first time, that β -cell failure and insulin resistance in patients with short-duration T2DM can be reversed by calorie restriction. These data are consistent with the hypothesis that abnormalities of insulin secretion and insulin resistance are caused by lipid accumulation in the pancreas and liver. This study challenged the hypothesis that improvement in glucose tolerance in patients with T2DM undergoing bariatric surgery is due to changes in incretin hormones.

Limitations

- Short duration of T2DM and short duration of follow-up;
- Small sample size;
- Study was unable to assess intracellular islet fatty acid content.

Further reading

Meijer R, van Wagensveld BA, Siebert CE et al. (2011). Bariatric surgery as a novel treatment for type 2 diabetes mellitus: a systematic review. *Arch Surg* **146**, 744–50.

T2DM: multiple risk factor intervention

Effect of a multifactorial intervention on mortality in type 2 diabetes.

AUTHORS: Gaede P, Lund-Andersen H, Parving H et al.

REFERENCE: *N Engl J Med* (2008) **358**, 580–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In high-risk patients with T2DM, multiple lifestyle and drug interventions had sustained beneficial effects on mortality and CV risk.

Impact

The results of this study highlighted that simple clinical interventions, available in most health-care systems, can have major benefits for patients with T2DM.

Aims

Prior to this study, this research group had shown in the Steno-2 study that intensified multifactorial intervention—with tight glucose regulation and the use of renin–angiotensin system blockers, aspirin, and lipid-lowering agents—reduced the risk of non-fatal CV disease in high-risk patients with T2DM (*N Engl J Med* (2003) **348**, 383–93). This extension of the original study aimed to assess whether this approach reduced total and CV mortality, 5.5y after the intervention ended.

Methods

Patients: 160 patients (from the original study); 130 provided data for this study (as 27 died, and three withdrew prior to this study).

Inclusion criteria:

- Age 40–65y with T2DM;
- Microalbuminuria.

Exclusion criteria:

- Stimulated serum C-peptide concentration <600pmol/L;
- Pancreatic insufficiency or diabetes 2° to pancreatitis;
- Alcohol abuse;
- Non-diabetic kidney disease;
- Malignancy;
- Life-threatening disease, with death probable within 4y.

Groups: All patients received renin–angiotensin system blockers and low-dose aspirin:

- Intensive therapy ($n = 80$): treatment with a view to achieving targets, including HbA_{1c} level <6.5%, fasting serum total cholesterol <4.5mmol/L, fasting serum triglyceride level <1.7mmol/L, and SBP <130mmHg;
- Conventional therapy ($n = 80$): multifactorial treatment, as per Danish Medical Association guidelines.

Primary outcome: Time to death from any cause.

Follow-up: 1° endpoint at 13.3y (mean F/U 5.5y).

Results

- Differences in risk factor levels were not significant at the end of the follow-up period;
- A total of 24 patients in the intensive therapy group died vs 40 in the conventional therapy group (HR 0.54; 95% CI 0.32–0.89; $p = 0.02$);
- Intensive therapy was associated with a lower risk of CV death (HR 0.43; 95% CI 0.19–0.94; $p = 0.04$) and of CV events (HR 0.41; 95% CI 0.25–0.67; $p < 0.001$);
- One patient in the intensive therapy group had progression to end-stage renal disease, as compared with six patients in the conventional therapy group ($p = 0.04$);
- Fewer patients in the intensive therapy group required retinal photocoagulation (RR 0.45; 95% CI 0.23–0.86; $p = 0.02$);
- Few major SEs were reported.

Discussion

The risk of death in the conventional therapy group was 50%, underscoring the high risk of death in this patient population. The absolute risk of death was reduced by 20%, which means that the NNT for the duration of the study to prevent one death was five patients. The absolute risk of CV death was reduced by 13%.

Limitations

- The study was not designed to identify which elements of the intensive therapy were beneficial;
- However, the authors provided evidence that statin and BP-lowering therapy might have had the largest effect in reducing CV risk.

Further reading

Gaede P, Vedel P, Larsen N *et al.* (2003). Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* **348**, 383–93.

Gaede P, Vedel P, Parving HH *et al.* (1999). Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* **353**, 617–22.

Emergency medicine

- Introduction 150
- Cervical spine trauma imaging 152
- Ankle injury imaging 154
- CT scanning in paediatric head injury 156
- Nasal diamorphine for analgesia in children 158
- Propofol for procedural sedation 160
- Fascia iliaca block after fractured neck of femur 162
- Tranexamic acid following trauma 164
- Ankle sprain management 166
- Managing acute whiplash injuries 168
- Hypothermia after VF cardiac arrest 170
- Septic shock: early goal-directed therapy 172
- Non-invasive ventilation for acute cardiogenic pulmonary oedema 174
- DVT: clinical decision rule and D-dimer testing 176

Introduction

Emergency medicine is a young field which has evolved from its humble origins in casualty departments focusing on minor injuries into a dynamic discipline encompassing critical and acute care for the complete spectrum of health problems. The specialty continues to adapt, in response to external pressures arising from increasing demand, demographic changes, service reconfigurations, and political contrivances such as the '4-h wait'. These developments, combined with the prodigious volume of patients attending emergency departments (EDs), offer a rich potential for research.

Despite the pivotal role of EDs within health systems, academic emergency medicine initially remained in its infancy outside of North America, lagging far behind other specialties. Professors Rod Little and David Yates were the pioneers of British emergency research, founding the MRC trauma unit and Emergency Medicine Research Society in 1984. From these auspicious beginnings, the research landscape in emergency medicine has been transformed, with major academic centres now established in Bristol, Edinburgh, Manchester, Warwick, and Sheffield. In common with American and Canadian research groups, high-quality emergency medicine studies are now regularly conducted and published in prestigious journals, and result in a powerful impact on patient care.

Emergencies occur at all ages, in diverse body systems, and with undifferentiated presentations. The challenge of reaching accurate early diagnoses and instigating rapid, effective treatments in these divergent conditions mandates a broad research approach comprising diagnostic, prognostic, and therapeutic studies. The following research papers reflect these diverse methods and represent groundbreaking studies which have shaped modern emergency medicine practice.

Cervical spine trauma imaging

The Canadian C-spine rule for radiography in alert and stable trauma patients.

AUTHORS: Stiell I, Wells G, Vandemheen K *et al.*

REFERENCE: JAMA (2001) **286**, 1841–8.

STUDY DESIGN: Prospective diagnostic cohort study developing a clinical prediction rule.

EVIDENCE LEVEL: 2b.

Key message

The Canadian C-spine rule is a highly sensitive decision rule for cervical (C-) spine radiograph imaging in alert and stable trauma patients.

Impact

This forms the basis for NICE imaging guidelines and is widely used internationally. It avoids unnecessary radiographs and facilitates early discontinuation of superfluous C-spine immobilization.

Aims

Despite the extremely low incidence of spinal fractures in neurologically normal patients, C-spine radiographs were used liberally, due to concerns about missing rare, but potentially devastating, injuries. This study aimed to produce a clinical decision rule (CDR) that would be highly sensitive for detecting C-spine injury but allow more efficient and selective use of radiography in alert and stable trauma patients.

Methods

Patients: 8,924 patients at ten EDs in Canada.

Inclusion criteria: Adult patients >16y with blunt trauma to the head or neck, stable vital signs, and Glasgow coma score (GCS) of 15.

Exclusion criteria: Injuries presenting >48h previously or known vertebral disease (e.g. ankylosing spondylitis).

Study design:

- Patients managed at the discretion of the attending doctor, including decisions regarding C-spine radiography;
- A standardized data set of 20 clinical findings were collected as potential prognostic factors, prior to radiography;
- Multivariate logistic regression analysis and recursive partitioning used to find the best combination of clinical variables which detected important C-spine injuries with the highest possible sensitivity and specificity.

Outcome measures:

- C-spine radiographs interpreted by blinded radiologists. Patients not undergoing imaging followed up clinically for 14d and recalled for clinical assessment and radiography, if any neck symptoms;

- Primary outcome: ‘clinically important C-spine injuries’ defined as fracture, dislocation, or ligamentous instability, demonstrated by diagnostic imaging.

Results

The final CDR comprised three questions: is there any high-risk factor present which mandates radiography?; is there any low-risk factor present that allows safe assessment of the range of motion?; is the patient able to actively rotate the neck 45° left and right? (See Table 6.1.)

Table 6.1 Summary of results

| Decision rule | Clinically significant C-spine injury | | |
|--------------------------|---------------------------------------|-------|-------|
| | Yes | No | Total |
| Positive | 151 | 5,041 | 5,192 |
| Negative | 0 | 3,732 | 3,732 |
| Total | 151 | 8,773 | 8,924 |
| Sensitivity (95% CI) | 100% (97.6–100.0) | | |
| Specificity (95% CI) | 42.5% (41.5–43.6) | | |
| PPV (95% CI) | 2.9% (1.71–1.77) | | |
| NPV (95% CI) | 100.0% (99.9–100.0) | | |
| Radiograph ordering rate | 58.2% | | |

Discussion

This study resulted in a simple CDR that rationalizes C-spine imaging in alert, stable patients at risk of neck injury. The Canadian C-spine rules have been prospectively validated in a range of settings, including a UK ED, with comparable sensitivity and specificity to that reported in this derivation study. A cluster randomized-controlled impact trial confirmed that the rule safely reduces X-ray ordering. Another decision rule of C-spine radiography in trauma is NEXUS, which was assessed in 34,069 patients (*N Engl J Med* (2000) 343, 94–9). A recent systematic review suggests the Canadian C-spine rule has greater sensitivity.

Problems

- A total of 3,281 potentially eligible cases not enrolled. As only minor differences in characteristics to included patients (slightly higher rates of arrival by ambulance or interhospital transfer), generalizability unlikely to be affected;
- Further 577 patients lost to follow-up. These patients were less severely injured and could introduce selection bias into accuracy estimates;
- C-spine radiographs only taken in 69% of patients studied, since considered unethical to X-ray patients at low risk of injury. Consequently, a potential for differential verification bias.

Ankle injury imaging

Accuracy of Ottawa ankle rules to exclude fractures of the ankle and mid-foot: systematic review

AUTHORS: Bachmann LM, Kolb E, Koller MT *et al.*

REFERENCE: *BMJ* (2003) 326, 417–23.

STUDY DESIGN: Systematic review and meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

The Ottawa ankle rules are highly sensitive for detecting ankle and fore-foot fractures. Implementation will reduce the number of unnecessary radiographs required in the assessment of ankle injuries.

Impact

The Ottawa ankle rules are widely accepted as a CDR to determine which patients with ankle injuries require radiographs. However, their application still varies considerably.

Aims

Ankle injury is a common presenting complaint to the ED, and it can be difficult to determine whether radiography is necessary to exclude fractures. This study aimed to summarize the evidence on the accuracy of the Ottawa ankle rules, a CDR for excluding ankle and mid-foot fractures.

Methods

Search strategy: A systematic evidence search was conducted, comprising bibliographic databases, reference lists, citation searching, and contact with study authors. There were no date or language restrictions.

Inclusion criteria: Any study assessing the diagnostic accuracy of the Ottawa ankle rules.

Exclusion criteria: 2×2 diagnostic accuracy contingency tables not reported.

- Studies with retrospective data collection, unknown blinding, or implementing modified versions of the decision rule were excluded from the meta-analyses.

Quality assessment: The methodological quality of eligible studies was assessed against established consensus guidelines.

Main outcome measure: Pooled negative likelihood ratio and pooled sensitivity.

Secondary outcome measure: Median and interquartile range of reported specificities.

Subgroups: Pooled results were reported, stratified according to the methodological quality and clinical characteristics.

Results

Table 6.2 Summary of results

| Outcome measure | |
|--|------------------|
| Pooled sensitivity, % (95% CI) | 97.6 (96.4–98.9) |
| Pooled negative likelihood ratio, % (95% CI) | 0.10 (0.06–0.16) |
| Specificity (median %, interquartile range) | 31.5 (23.8–44.4) |
| Probability of fracture following negative result, % (95% CI)* | 1.73 (1.05–2.75) |

*Assumed fracture prevalence of 15%.

- A total of 32 studies were identified which met the inclusion criteria.
- Of these, 27 studies with 15,581 patients were pooled in the meta-analyses. (See Table 6.2.)
- Pooled sensitivity did not differ meaningfully with differing characteristics of the presenting population (age, fracture prevalence, time from injury to assessment);
- Pooled negative likelihood ratios were slightly worse in studies with lower risk of bias and higher fracture prevalences.

Discussion

This study was the first to summarize the performance of the Ottawa ankle rules across a disparate range of validation studies. It confirmed that their introduction should reduce the number of ankle radiographs, with a low risk of missing fractures. Additional studies have subsequently studied the impact of introducing the rules, confirmed their cost-effectiveness, and demonstrated similar pooled sensitivity in paediatric populations. However, despite this evidence, application and compliance still vary considerably.

The range of specificities in the included studies was substantial, with implications for the number of unnecessary X-rays potentially avoided. Possible explanations for this variation include differences in training, experience, and cultural expression of pain.

Problems

- No study protocol was prespecified, with a consequent potential for bias arising from post hoc changes in methodology;
- Although a comprehensive literature search was performed, publication bias could have arisen from non-inclusion of grey literature;
- The rules may be unreliable when clinical assessment is difficult, or in the minority of patients in whom gross swelling makes it impossible to palpate the posterior edge of the malleoli.

CT scanning in paediatric head injury

CHALICE (Children's Head Injury Algorithm for the prediction of Important Clinical Events): Derivation of the children's head injury algorithm for the prediction of important clinical events decision rule for head injury in children.

AUTHORS: Dunning J, Patirck Daly J, Lomas JP *et al.*

REFERENCE: *Arch Dis Child* (2006) **91**, 885–91.

STUDY DESIGN: Prospective diagnostic cohort study.

EVIDENCE LEVEL: 2b.

Key message

The CHALICE CDR is highly sensitive for identifying children with significant head injuries who should undergo CT scanning.

Impact

The CHALICE CDR was incorporated into the NICE head injury guidance from 2007. Retrospective external validation studies suggest implementation of the rule results in a moderate to large increase in CT scan rates and satisfactory sensitivity. However, prospective validation and impact studies are awaited.

Aims

Up to half a million children attend UK EDs, following head injuries each year. However, mortality is low (estimated 0.2%), and there is a small, but well-defined, risk of leukaemia and brain cancer, attributable to exposure to radiation from CT. This study aimed to develop a sensitive CDR for identifying children at high risk, following injury, to undergo CT scanning, and to allow safe discharge of others.

Methods

Patients: 22,772 consecutive children in ten EDs in North West England.

Inclusion criteria:

- Children <16y with a history or signs of injury to the head.

Study design:

- Followed 1999 Royal College of Surgeons head injury guidelines.
- A standardized data set of 40 demographic, clinical, injury, and management characteristics was collected as potential prognostic factors.
- Multivariate recursive partitioning used to find the best combination of highly sensitive predictors for clinically significant intracranial injury;
- Reliability of each predictor assessed in subsample of 412 children.

Primary outcome measure:

- 'Clinically significant intracranial injury': a composite endpoint comprising death from head injury, requirement for neurosurgery, or any new acute traumatic intracranial lesion on CT head scan (excluding non-depressed skull fractures).

Secondary outcome measures:

- Presence of skull fracture, hospital admission.

Results

- CDR included 14 predictors (six history, five examination, three mechanism of injury). CT recommended, if any criteria present. (See Table 6.3.)

Table 6.3 Summary of results

| Outcome measure | No clinically significant head injury | Clinically significant head injury | Total |
|---------------------------|---------------------------------------|------------------------------------|--------|
| CHALICE negative | 19,558 | 4 | 19,562 |
| CHALICE positive | 2,933 | 227 | 3,210 |
| Total | 22,491 | 281 | 22,772 |
| Sensitivity (95% CI) | 98.6% (96.4–99.6) | | |
| Specificity (95% CI) | 86.9% (86.5–87.4) | | |
| PPV (95% CI) | 7.18% (6.31–8.14) | | |
| NPV (95% CI) | 99.9% (99.9–100) | | |
| CT ordering rate (95% CI) | 14.1% (13.6–14.6) | | |

Discussion

A promising CDR that is highly sensitive, but easy to use, with clear face validity. Derivation studies typically demonstrate excellent performance that is not replicated in other study populations. Despite supportive retrospective external validation and its adoption by NICE, these results should be treated cautiously, until a prospective validation is conducted. Several other CDRs for paediatric head injury have been developed, including the PECARN rule which has undergone temporal validation in the same population. These have shown similar diagnostic utility to CHALICE for the detection of clinically significant head injury.

Problems

- Number and characteristics of non-recruited, but eligible, children were unreported, but unlikely to be a major barrier to generalizability;
- CDR primarily applicable to minor head injuries with GCS 14–15. Inclusion of moderate and severe head injury patients may have introduced spectrum effects influencing the sensitivity and specificity;
- Differential verification bias could have arisen, 2° to the composite reference standard;
- In some cases, study proformas were completed retrospectively, unblinded to CT scan results, potentially introducing test review bias;
- Unclear if CT scans were interpreted blinded to CHALICE predictors, raising the possibility of diagnostic review bias;
- Clinical effectiveness, acceptability, reproducibility, usability, and cost-effectiveness should also be assessed in implementation RCTs.

Nasal diamorphine for analgesia in children

Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical fractures.

AUTHORS: Kendall J, Reeves B, Latter V.

REFERENCE: *BMJ* (2001) 322, 261–5.

STUDY DESIGN: Multicentre, open-label, parallel-group randomized-controlled trial.

EVIDENCE LEVEL: Ib.

Key message

Nasal diamorphine provides effective and acceptable analgesia for children in acute pain from fractures.

Impact

Nasal diamorphine is now used in many EDs as the preferred choice of analgesia for children with severe pain who do not need immediate IV access.

Aims

To compare the effectiveness and acceptability of nasal diamorphine spray and intramuscular (IM) morphine for analgesia in children with pain from a suspected fracture.

Methods

Patients: 413 children in eight UK EDs.

Inclusion criteria:

- Children aged 3–16y with clinical fracture of upper or lower limb.

Main exclusion criteria:

- Need for immediate IV access, head injury, intolerance to opioids, upper respiratory tract infection (URTI), or blocked nose.

Groups: Rescue analgesia with IM morphine 0.2mg/kg was given to any child who was still in extreme pain 20–30min after treatment.

- Intervention group: diamorphine 0.1mg/kg delivered by a nasal spray device ($n = 204$ patients);
- Control group: IM morphine 0.2mg/kg ($n = 200$ patients).

Outcome measures:

- Primary outcome: pain assessment by patients, parents, and staff, using the Wong Baker face pain scale (1–6) before treatment and after 5, 10, 20, and 30min;
- Secondary outcomes: nurses' and parents' assessment of acceptability of treatment (4-point ordinal score, ranging from no obvious discomfort to unacceptable). Adverse events observed within 30min of treatment.

Results

- Nasal diamorphine relieved pain faster than IM morphine, with lower pain scores at 5, 10, and 20min, but no difference at 30min (χ^2 test for trend of distribution of patients' Wong Baker pain scores: p -value 0.04 at 5min, 0.003 at 10min, 0.002 at 20min, 0.20 at 30min);
- Nasal diamorphine was much more acceptable than IM morphine, as assessed by patients, parents, and staff (χ^2 tests for trend $p < 0.01$);
- No unexpected or serious adverse effects were seen in either group.

Discussion

Children in acute pain need prompt and effective analgesia. Injections may be painful and distressing; oral analgesia may be inadequate, and rectal administration has limited acceptability, with slow and variable onset of analgesia. This trial showed that nasal diamorphine gives effective and acceptable analgesia in children with limb fractures, avoiding painful injections in patients who do not need immediate IV access.

Few EDs have the nasal spray devices used in this trial, so nasal diamorphine is usually given dissolved in 0.2mL of saline and dripped into the nose from a syringe. Since this trial, medicinal diamorphine has been in short supply in the UK and is not available in all countries. Further studies have demonstrated the effectiveness of nasal administration of other opioids such as alfentanyl.

Problems

- The trial was not blinded or placebo-controlled, because it was thought unethical to give dummy IM injections in the nasal diamorphine group. This could introduce performance bias or outcome ascertainment bias;
- Despite claiming an intention-to-treat analysis, 2.2% of patients were excluded from analyses after enrolment. This low level of missing data is unlikely to result in selection bias;
- IM injections are painful, with variable drug absorption, and consequently are rarely used, compared with IV opioids. However, they still play a role in certain patients (e.g. paediatric), particularly when other routes of administration are unavailable.

Propofol for procedural sedation

Propofol versus midazolam/fentanyl for reduction of anterior shoulder dislocation

AUTHORS: Taylor D, O'Brien D, Ritchie P *et al.*

REFERENCE: *Acad Emerg Med* (2005) 12, 13–19.

STUDY DESIGN: Parallel-group RCT.

EVIDENCE LEVEL: 1b.

Key message

Propofol provides quicker recovery from procedural sedation than midazolam/fentanyl, but with similarly substantial rates of adverse respiratory events.

Impact

First reasonably powered trial to suggest benefit of propofol over midazolam. Propofol now widely used in emergency procedural sedation.

Aims

Sedation and analgesia for painful emergency procedures are commonly required, traditionally achieved using midazolam and opioids. Propofol is a potent and short-acting IV anaesthetic agent which may offer a more rapid onset of sedation, improved muscle relaxation, better analgesia, and quicker recovery. This trial aimed to compare recovery times and adverse events when using propofol or midazolam/fentanyl for a common ED procedure.

Methods

Patients: 86 patients at three Australian EDs.

Inclusion criteria:

- Adult patients aged >18y with anterior shoulder dislocation.

Exclusion criteria:

- Additional injuries, allergy to study drugs, pregnancy, or contraindications to sedation (<4h since food/fluid intake, <6h since alcohol intake, anticipated difficult airway).

Groups: All received titrated IV morphine and 10mg of metoclopramide prior to sedation, supplemental oxygen (O_2), and monitoring. Initial shoulder reduction attempted using the Kocher's method, with other methods subsequently used as required.

- Propofol ($n = 48$): slow IV bolus of propofol, titrated to clinical sedation. Supplementary intermittent boluses of propofol, as required;
- Midazolam/fentanyl ($n = 38$): 1.25 micrograms/kg IV fentanyl, followed after 3min by slow IV midazolam bolus, titrated to clinical sedation. Supplementary intermittent boluses of midazolam, as required.

Primary outcomes:

- Time from shoulder reduction to first wakening and to full consciousness. Muscle tone and ease of shoulder reduction.

Secondary outcomes:

- Shoulder reduction failure and number of different manoeuvres required. Adverse events, including respiratory depression, memory of procedure, hypotension, vomiting, and aspiration.

Results**Table 6.4** Summary of results

| Endpoint | Propofol (n = 48) | Midazolam/fentanyl (n = 38) | p |
|--|----------------------|--------------------------------|--------|
| First awaking time, min (95% CI) | 3.4 (2.5–4.3) | 8.0 (3.8–12.3) | 0.1 |
| Full wakefulness time, min (95% CI) | 6.8 (5.5–8.1) | 28.5 (20.9–36.1) | <0.001 |
| Muscle tone at first reduction attempt (1 = flaccid to 5 = impedes relocation) | 2.5 (2.2–2.8) | 3.0 (2.6–3.4) | 0.08 |
| Ease of reduction (1 = very easy to 5 = very difficult) | 2.0 (1.7–2.3) | 2.4 (2.1–2.8) | 0.05 |
| Respiratory depression, % (95% CI) | 22.9 (12.5–37.7) | 15.8 (6.6–31.9) | 0.15 |

- Reduction failure rate and the number of relocation techniques required did not vary meaningfully between the two sedation options;
- Respiratory depression common in both groups. Simple airway manoeuvres or brief assisted ventilation was sufficient. No patients required intubation;
- Other adverse events were rare in both groups. (See Table 6.4.)

Discussion

This study indicates a potential benefit from a more rapid recovery following ED propofol sedation, but highlights a concomitant risk of respiratory depression. Both should be administered by suitably trained individuals. Further small RCTs have suggested similar results in cardioversion and other orthopaedic reductions. Procedural sedation is now firmly established in UK EDs. With the recent introduction of ketamine and ketofol sedation, factorial head-to-head trials are necessary to determine the optimum strategy.

Problems

- Only powered to detect moderate difference in time to recovery. Important differences in respiratory complications may exist but did not reach significance, due to an inadequate sample size;
- Propofol has a distinctive appearance. As physicians reported outcomes during administration, it is unlikely complete blinding was achieved. Performance/information biases may have influenced the results;
- Differences in baseline characteristics of groups, 2° to a small sample, may confound unadjusted effect estimates.

Fascia iliaca block after fractured neck of femur

Fascia iliaca compartment blockade for acute pain control in hip fracture patients.

AUTHORS: Foss N, Kristensen B, Bundgaard M *et al.*

REFERENCE: *Anesthesiology* (2007) **106**, 773–8.

STUDY DESIGN: Parallel-group placebo-controlled trial.

EVIDENCE LEVEL: 1b.

Key message

Fascia iliaca compartment blockade (FICB) offers superior pain relief to opioid analgesia, following hip fractures.

Impact

This small RCT provides the best evidence on the effectiveness of FICB, which is increasingly used as the first-line pain relief strategy acutely, following hip fracture.

Aim

Hip fractures are associated with severe pain, and parenteral opioids have traditionally been used for preoperative analgesia, despite concerns regarding SEs and suboptimal pain relief. This study aimed to compare the effectiveness of FICB in reducing hip fracture pain, compared with systemic opioids.

Methods

Patients: 48 patients from a single tertiary hospital in Denmark.

Inclusion criteria:

- Clinical signs of hip fracture.

Exclusion criteria:

- Previous surgery to affected hip, confusion, regular prescribed opioids, morphine intolerance, infection at potential FICB injection site, non-confirmation of hip fracture on X-ray.

Groups: All patients were administered continuous nasal O₂ at 2L/min and oral paracetamol 30min after receiving the allocated treatment. Patients also received 2.5mg of IV morphine, as required.

- FICB group: FICB with 1.0% mepivacaine and 1:200,000 epinephrine administered using a landmark technique. Placebo IM injection of isotonic saline;
- IM opioid group: placebo FICB with 0.9% saline. IM injection of 0.1mg/kg of morphine.

Outcome measures: All outcomes were assessed at 30, 60, and 180min post-intervention.

- Primary outcomes: difference in pain scores at rest and on passively elevating the fractured leg to 15°. Pain was measured on 10-point ordinal scales, ranging from 0 = none to 10 = worst imaginable;
- Secondary outcomes: sedation and nausea, measured on 4-point ordinal scales, ranging from 0 = none to 3 = severe. O₂ saturations.

Results

- Successful nerve blockade was registered in 67% of patients in the FICB group;
- FICB appreciably improved pain scores at rest and on movement at all time points, compared with IM morphine, reaching statistical significance at 60 and 180min;
- Significantly more patients were sedated at 180min post-intervention in the IM morphine group (one vs six patients, $p = 0.05$);
- IM morphine patients had slightly lower O₂ saturations, although this was not clinically or statistically significant;
- There were no differences in nausea and vomiting between groups;
- There was one episode of haematemesis in the FICB group, but no adverse events related to nerve blockade or opioid administration.

Discussion

FICB is an inexpensive and readily learnt procedure, demonstrating good pain relief for hip fractures. Sixty-seven percent of studied patients received effective nerve blocks, and ultrasound guidance may offer an alternative method to improve success rates. Insertion of a catheter for continuous infusion or additional boluses of a local anaesthetic is also possible. Although observational studies have reported comparable results to this study, further larger RCTs are required. Additionally, alternative methods of regional anaesthesia blocks have been advocated, including femoral nerve blocks and 3-in-1 (obturator, femoral, and lateral femoral cutaneous nerves) blocks. Ongoing trials are evaluating the roles of these techniques, in comparison to FICB.

Problems

- Noticeable imbalances in baseline characteristics existed between the study groups. These chance differences are expected, given the small sample size, but could have confounded the results;
- The study was not large enough to detect rare adverse events;
- Important endpoints, including hospital length of stay, confusion, and mortality, were not considered;
- The study was described as double-blind, but it is not clear whether outcome assessment was masked. The risk of ascertainment bias is therefore unclear.

Tranexamic acid following trauma

CRASH-2 (Clinical Randomisation of an Anti-fibrinolytic in Significant Haemorrhage 2): Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage: a randomised, placebo-controlled trial.

AUTHORS: Shakur H, Roberts I, Bautista R et al.

REFERENCE: *Lancet* (2010) 376, 23–32.

STUDY DESIGN: Multicentre, parallel-group, randomized, placebo-controlled trial.

EVIDENCE LEVEL: 1b.

Key message

Early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding safely reduces the risk of death from haemorrhage.

Impact

Tranexamic acid is an inexpensive, easily used, and relatively safe drug that is now routinely used worldwide in civilian and military trauma practice.

Aims

Injuries are a major global cause of mortality, predicted to become the third leading cause of death by 2020. Tranexamic acid is an anti-fibrinolytic agent known to reduce the need for blood transfusion following elective surgery. This study aimed to assess the effects of early administration of tranexamic acid on mortality in trauma patients with, or at risk of, significant haemorrhage.

Methods

Patients: 20,211 patients at 274 hospitals in 40 countries.

Inclusion criteria: Adult trauma patients, within 8h of injury, with significant haemorrhage (SBP <90mmHg ± HR >110bpm) or considered clinically at risk of significant haemorrhage.

Exclusion criteria: Contraindications to tranexamic acid (e.g. allergy).

Groups:

- Intervention group: IV loading dose of 1g of tranexamic acid infused over 10min, followed by 1g infused over 8h;
- Control group: matching infusion regimen of placebo (0.9% saline).

Primary outcomes:

- All-cause and cause-specific (bleeding, vascular occlusion, multiorgan failure, head injury, other) inpatient death within 4wk of injury.

Secondary outcomes:

- Vascular occlusive events, surgical interventions, receipt of blood transfusions, units of blood products transfused, and dependency at hospital discharge or 28d (modified Oxford Handicap Scale, dichotomized into favourable and unfavourable outcome).

Results

Table 6.5 Summary of results

| Outcome | Placebo | Tranexamic acid | RR |
|-------------------------|---------|-----------------|------------------|
| Primary outcomes | | | |
| All-cause mortality | 16.0% | 14.5% | 0.91 (0.85–0.97) |
| Death from bleeding | 5.7% | 4.9% | 0.85 (0.76–0.96) |

- Small, but clinically and statistically significant, reductions in all-cause and bleeding-specific mortality; the NNT was 67;
- Cause-specific deaths from multiorgan failure, head injury, or other causes did not differ significantly across study groups (see Table 6.5);
- No significant differences in secondary outcomes of vascular occlusive events, transfusion or surgery need, and unfavourable outcome;
- A post hoc exploratory subgroup analysis, examining the effect of time from injury to tranexamic acid administration on death from bleeding, suggested early treatment significantly reduced the risk of death due to bleeding (≤ 1 h from injury: RR 0.68, 95% CI 0.57–0.82; 1–3h from injury: RR 0.79, 95% CI 0.64–0.97). Treatment after 3h seemed to increase the risk of death due to bleeding (RR 1.44, 95% CI 1.12–1.84).

Discussion

This trial was a landmark trial in trauma, establishing tranexamic acid as an effective hospital-based treatment for traumatic haemorrhage. The trial had excellent internal validity with well-balanced treatment groups, complete follow-up, and hard objective outcomes, precluding confounding, selection bias, and information bias. Despite clearly demonstrating a mortality benefit, laboratory coagulation parameters were not measured, and the mechanism by which tranexamic acid improves mortality is consequently uncertain.

Problems

- Subgroup analysis suggesting a benefit from early administration of tranexamic acid, but increased risk of death after 3h, was post hoc and did not meet established criteria to suggest a strong subgroup effect. This finding should be considered as hypothesis-generating;
- The majority of recruitment sites were in low- and middle-income countries (vs developed world trauma centres with access to massive blood transfusion protocols and blood products).

Ankle sprain management

CAST (Collaborative Ankle Support Trial): Mechanical supports for acute, severe ankle sprain: a pragmatic, multicentre, randomised controlled trial.

AUTHORS: Lamb S, Marsh J, Hutton J *et al.*

REFERENCE: *Lancet* (2009) **373**, 575–81.

STUDY DESIGN: Multicentre, pragmatic, parallel-group RCT.

EVIDENCE LEVEL: 1b.

Key message

A short period of immobilization in an Aircast, or below-knee cast, results in a faster recovery than tubular compression bandages, following a severe ankle sprain.

Impact

This study was the largest and most robust clinical trial to date, evaluating management following acute ankle sprains. Contrary to accepted clinical opinion, immobilization was found to be more effective than functional treatment. Whether these findings are translated into routine practice waits to be seen.

Aims

Ankle sprains are a common presentation to EDs, accounting for up to 5% of attendances. This study aimed to assess the effectiveness of four alternative methods of mechanical support (Aircast brace, Bledsoe boot, 10d below-knee cast, double-layer elastic tubular bandage) in promoting recovery, following acute severe sprains.

Methods

Patients: 584 patients at eight EDs in England.

Inclusion criteria: Adult patients aged over 16y with acute ankle sprains and the inability to weight-bear for at least 3d post-injury.

Exclusion criteria: Ankle fractures, subacute injuries occurring >7d previously, or contraindications to immobilization.

Groups:

- Control: tubular compression bandage, with progressive weight-bearing and activity;
- Aircast: splints sized and applied to manufacturer's instructions;
- Below-knee cast: synthetic, non-flexible cast applied for 10d;
- Bledsoe boot: sized and applied to manufacturer's instructions.

Primary outcome:

- Self-reported quality of ankle function at 3, 6, and 9mo, measured using the Foot and Ankle Outcome Score (FAOS) quality subscale.

Secondary outcomes:

- Additional FAOS subscale scores (pain, activities of daily living (ADLs), symptoms, sports), generic QoL (short-form 12), pain (visual analogue scale), and additional treatments required.

Results**Table 6.6** Summary of results

| FAOS quality of ankle function subscale score | Tubigrip® (n = 144) | Below-knee cast (n = 142) | Aircast (n = 149) | Bledsoe boot (n = 149) |
|---|------------------------|---|----------------------|---------------------------|
| | Mean score | Mean difference from Tubigrip® score (95% CI) (adjusted for age, gender, and baseline score) | | |
| 1mo | 43 | 6 (0.1–11.8) | 5 (–1.0 to 10.7) | 2 (–3.9 to 7.6) |
| 3mo | 54 | 9 (2.4–15.0) | 8 (1.8–14.2) | 6 (0–12.3) |
| 9mo | 65 | 6 (–0.7 to 13.2) | 6 (–0.9 to 13.0) | 4 (–2.9 to 10.8) |

- Significant difference in quality of ankle function was evident at 3mo following below-knee cast or Aircast immobilization, compared with tubular bandage treatment;
- Long-term treatment benefits of below-knee cast or Aircast were not confirmed, with only small improvements in 9mo of FAOS subscale scores reported that did not reach minimally important clinical differences or statistical significance. (See Table 6.6.)

Discussion

First study to directly compare common treatments used for immobilization, following ankle sprain, to management with a tubular bandage. The unexpected results were at variance with the consensus that functional management provides superior recovery. As a pragmatic trial, the effect estimates will reflect those expected in normal clinical practice, rather than the inherent efficacy of each intervention. However, the commonest reason for declining entry into the trial was refusal to accept a below-knee cast (59%), suggesting compliance could be problematic. Interventions were compared to tubular bandages individually. Further trials needed to directly compare Aircasts and below-knee cast immobilization.

Problems

- Loss to follow-up was substantial (34% of participants). However, as there were no systematic differences between completers and non-completers and an intention-to-treat analysis was performed, selection bias is unlikely;
- The impossibility of blinding and use of self-reported outcome assessment could have resulted in ascertainment bias;
- Results are relatively imprecise with wide CIs consistent with either a beneficial or null effect of interventions at 9mo.

Managing acute whiplash injuries

MINT (Managing Injuries of the Neck Trial): Emergency department treatments and physiotherapy for acute whiplash: a pragmatic, two-step, randomised controlled trial.

AUTHORS: Lamb S, Gates S, Williams M *et al.*

REFERENCE: *Lancet* (2013) **381**, 546–56.

STUDY DESIGN: Pragmatic cluster randomized trial, with additional nested individual randomized controlled subtrial.

EVIDENCE LEVEL: 1b.

Key message

Active management ED consultations following whiplash provide no additional benefits over usual care in reducing neck symptoms.

Impact

This study adds to the evidence base for the management of whiplash, demonstrating that usual ED care with a single physiotherapy advice session for persisting symptoms is currently the most effective and efficient management strategy.

Aims

The aim of this study was to determine if initial active management consultations in the ED were superior to usual consultations.

Methods

Patients:

- A total of 3,851 patients in 15 UK EDs. Each ED was assigned as a different cluster with subsequent recruitment of incident whiplash cases.

Inclusion criteria:

- Adults aged >18y with an acute whiplash injury (<6wk duration).

Exclusion criteria:

- GCS <13, non-transient loss of consciousness, any fracture or dislocation, patients requiring hospital admission, psychiatric illness.

Groups:

- Intervention group: active management ED consultation comprising: counselling, exercise, and analgesia advice, and a copy of a patient education booklet (*The Whiplash book*);
- Control group: usual ED consultation and provision of standard patient leaflet.

Outcome measures:

- Primary outcome: neck disability index at 4, 8, and 12mo;
- Secondary outcomes: self-rated improvement in neck symptoms, QoL (short form-12 and EQ-5D scores), NHS and private health-care use, compensation claims, and work days lost.

Results

Table 6.7 Summary of results

| Neck disability score | Usual care (<i>n</i> = 1,598) | Active management (<i>n</i> = 2,253) | Difference | <i>p</i> |
|-----------------------|-----------------------------------|--|-------------------|----------|
| 3mo | 20.4 (17.2) | 21.5 (17.6) | 0.5 (−2.1 to 3.0) | 0.71 |
| 8mo | 16.0 (16.4) | 16.6 (16.5) | 0.8 (−1.6 to 3.1) | 0.52 |
| 12mo | 14.4 (16.0) | 14.4 (15.9) | 0.5 (−1.5 to 2.5) | 0.64 |

(Range 0–100; low score indicates little disability; mean, SD)

- No clinically or statistically significant differences were observed in secondary outcomes examining self-reported change in neck symptoms, QoL, or work days lost (see Table 6.7);
- Economic evaluation showed active management was associated with higher costs and fewer quality-adjusted life-years (QALYs) than usual care.

Discussion

An additional individual patient RCT and economic evaluation examined subsequent care, comparing a single physiotherapy advice session with an 8-wk physiotherapy programme. The physiotherapy programme showed a small, non-sustained effect on neck disability and was not cost-effective. Together, these trials strongly suggest that a stepped care approach is not more effective than simple reassurance and exercise advice. Although cluster randomized trials have well-known limitations, such a design was unavoidable, given the risk of contamination between treatment groups and the need to train health-care providers in the intervention. The study followed best practice with monitoring for post-randomization recruitment bias, use of adjusted intention-to-treat analyses accounting for clustering, and blinded outcome assessment.

Problems

- Cluster randomized trials are susceptible to selection bias from differential post-randomization recruitment;
- Loss to F/U was substantial, with multiple imputation used to facilitate an intention-to-treat analysis. Attrition bias is possible, if data were not missing at random.
- The economic evaluation is from an NHS NICE perspective and therefore does not account for societal costs of lost productivity arising from whiplash.

Hypothermia after VF cardiac arrest

Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.

AUTHORS: Hypothermia after Cardiac Arrest Study Group.

REFERENCE: *N Engl J Med* (2002) **346**, 549–56.

STUDY DESIGN: Multicentre, parallel-group RCT.

EVIDENCE LEVEL: 1b.

Key message

Mild therapeutic hypothermia improves neurological outcome and reduces mortality following cardiac arrest 2° to VF or ventricular tachycardia (VT).

Impact

The benefits of hypothermia following cardiac arrest with a shockable rhythm were confirmed in a 2009 Cochrane systematic review, and cooling is now the established standard of care.

Aims

Cardiac arrest is a leading cause of death in Europe, with an estimated 375,000 cases annually. Thirty-one to 65% of cardiac arrests are due to VF, with <20% of such patients surviving an out-of-hospital arrest. Animal studies suggested mild hypothermia reduced brain damage after cardiac arrest, and this study aimed to determine if mild systemic hypothermia reduced death and disability after resuscitation from cardiac arrest due to VF or non-perfusing VT.

Methods

Patients: 275 patients from nine hospitals in five Western European countries.

Inclusion criteria:

- Adult patients between 18 and 75y;
- Return of spontaneous circulation following a witnessed cardiac arrest due to VF or pulseless VT;
- An interval of 5–15min from the patient's collapse to the first attempt at resuscitation by emergency medical personnel;
- An interval of <60min from collapse to restoration of spontaneous circulation.

Main exclusion criteria: Hypothermia <30°C on admission, shock for >30min after return of spontaneous circulation, response to verbal commands after return of spontaneous circulation, terminal illness.

Groups:

- Intervention group: standard intensive care with mild hypothermia to 32–34°C for 24h, using a cold air cooling blanket and ice packs;
- Control group: standard intensive care with normothermia.

Outcome measures:

- Primary outcome: favourable neurological outcome at 6mo (defined as Pittsburgh cerebral performance categories of good recovery or moderate disability);
- Secondary outcomes: all-cause mortality at 6mo, complications within 7d.

Results**Table 6.8** Summary of results

| Outcome | Normothermia (n = 137) | Hypothermia (n = 136) | ARR, % (95% CI) | Risk ratio, RR (95% CI) |
|--|---------------------------|--------------------------|---------------------------|----------------------------|
| Favourable neurological outcome at 6mo | 39.4% | 55.1% | 15.7% (3.9–27.2) | 1.40 (1.08–1.81) |
| Mortality at 6mo | 55.1% | 40.9% | –14.2% (–2.4 to –25.6) | 0.74 (0.58–0.95) |

- To prevent one unfavourable neurologic outcome, six patients would need to be treated with hypothermia (NNT 95% CI 4–25). Seven patients would need to be treated with hypothermia to prevent one death (NNT 95% CI 4–33);
- The complication rate was similar in both study groups, with no statistically significant differences. (See Table 6.8.)

Discussion

Prior to this study, there were no therapies with proven benefits in reducing brain damage after cardiac arrest. Further RCTs have corroborated these findings, and a recent Cochrane systematic review and meta-analysis have confirmed the effectiveness of mild hypothermia following VF/VT arrests. Further studies are now required to delineate the optimum duration, method, and depth for cooling. A number of small RCTs have additionally examined the role of implementing pre-hospital cooling, with inconclusive results.

Problems

- It was not possible to blind health-care workers to group allocation, which may introduce performance bias tending to exaggerate effect estimates;
- The trial enrolled only a small subset of cardiac arrest patients, and the role of hypothermia in cardiac arrests 2° to asystole and pulseless electrical activity is uncertain. The high mortality rate in such conditions may challenge future trials, because of the large sample sizes that would be required to detect a significant difference in outcomes.

Septic shock: early goal-directed therapy

Early goal-directed therapy in the treatment of severe sepsis and septic shock.

AUTHORS: Rivers E, Nguyen B, Havstad S *et al.*

REFERENCE: *N Engl J Med* (2001) **345**, 1368–77.

STUDY DESIGN: Parallel-group, open RCT.

EVIDENCE LEVEL: 1b.

Key message

Early goal-directed therapy (EGDT) may reduce the high mortality of severe sepsis and septic shock.

Impact

This work has stimulated many other studies and the international 'Surviving sepsis' campaign to reduce the number of deaths from sepsis. However, full uptake of EGDT has remained limited.

Aims

Goal-directed therapy for septic shock involves manipulating cardiac preload, afterload, and contractility to improve O_2 delivery and correct tissue hypoxia. Goal-directed therapy had previously been studied in critical care settings, with conflicting results. This study aimed to assess the value of earlier instigation in the ED, prior to intensive care admission.

Methods

Patients: 263 patients at one ED in a tertiary care hospital in the USA.

Inclusion criteria: Adults aged ≥ 18 y with suspected infection, systemic inflammatory response syndrome (SIRS), and: SBP ≤ 90 mmHg after fluid challenge (crystalloid 20–30mL/kg over 30min), or blood lactate ≥ 4 mmol/L.

Main exclusion criteria: 1° diagnosis of acute medical illness (CVA, ACS, etc.), immunosuppression, uncured cancer, non-infective causes of SIRS.

Groups:

- EGDT: treated for at least 6h in the ED with continuous central venous O_2 saturation (SCVO₂) monitoring. Protocolized resuscitation, including:
 - Crystalloid bolus (500mL every 30min until central venous pressure (CVP) 8–12mmHg);
 - Vasoactive drugs if mean arterial pressure (MAP) < 65 mmHg or > 90 mmHg;
 - Continuous SCVO₂ monitoring: if SCVO₂ $< 70\%$, red cell transfusion to haematocrit $\geq 30\%$, then IV dobutamine 2.5–20 micrograms/kg/min;
- Standard therapy: treated at the attending clinicians' discretion, according to a guideline targeting CVP 8–12mmHg, MAP ≥ 65 mmHg, and urine output ≥ 0.5 mL/kg/h;
- Critical care physicians took over care of all patients after admission from the ED and were unaware of patients' group allocations.

Primary outcome: In-hospital mortality.

Secondary outcomes: Physiological and biochemical resuscitation endpoints, multiorgan dysfunction scores, coagulation-related variables, administered treatments, use of health-care resources.

Results

Table 6.9 Summary of results

| Therapy | Standard (n = 133) | EGDT (n = 130) | RR (95% CI) |
|-----------------------|--------------------|----------------|------------------|
| In-hospital mortality | 59 (46.5%) | 38 (30.5%) | 0.58 (0.38–0.87) |

Percentages were calculated by the Kaplan–Meier product-limit method.

- NNT 6.6, 95%CI 3.8–28.9;
- In the first 6h, the EGDT group received more fluids, red cell transfusions, and inotropic support than the standard therapy group ($p < 0.001$), but similar numbers had vasopressors ($p = 0.62$) and mechanical ventilation ($p = 0.90$);
- At 6h after enrolment, physiological and biochemical resuscitation endpoints were appreciably (and statistically significantly) improved in the EDGT group (see Table 6.9);
- Other secondary outcomes of coagulopathy indices and organ dysfunction scores also significantly more favourable in the EGDT group.

Discussion

Severe sepsis and septic shock are common, with high mortality and many deaths associated with sudden CV collapse. This study suggests that EGDT with rapid correction of fluid deficit and tissue hypoxia improves mortality. Subsequent observational studies attempting to replicate these findings have shown inconsistent results. Several international multicentre trials are ongoing which should definitively confirm the role of EGDT in sepsis. Despite the large effect estimates reported in this milestone study, surveys have found that EGDT is not routinely practised in EDs. Reported barriers to implementation include internal validity concerns, resource constraints, and the complexity of the intervention.

Problems

- Although intensive care staff were blinded to treatment allocation, care delivered was unmasked. Consequently, a high risk of performance bias expected to exaggerate the mortality benefit;
- Standard of EGDT demonstrated in a single site may be beyond the capabilities and resources of some EDs, limiting applicability.

Non-invasive ventilation for acute cardiogenic pulmonary oedema

3-CPO (3 Interventions in Cardiogenic Pulmonary Oedema): Noninvasive ventilation in acute cardiogenic pulmonary edema.

AUTHORS: Gray A, Goodacre S, Newby D et al.

REFERENCE: *N Engl J Med* (2008) **359**, 142–51.

STUDY DESIGN: Parallel-group, pragmatic RCT.

EVIDENCE LEVEL: 1b.

Key message

In adults with acute cardiogenic pulmonary oedema, non-invasive ventilation (NIV) results in a more rapid improvement in respiratory distress than standard O₂ therapy, but has no effect on short-term mortality.

Impact

This study clarified the position of NIV in the management of cardiogenic pulmonary oedema, defining its role as an adjuvant treatment in patients with severe respiratory distress.

Aims

A meta-analysis of small RCTs had suggested continuous positive airways pressure (CPAP) and non-invasive positive pressure ventilation (NIPPV) reduced mortality and the need for intubation, compared to simple O₂ therapy in acute cardiogenic pulmonary oedema. However, the validity of the component studies was uncertain, and this study aimed to determine whether NIV (CPAP or NIPPV) improved survival, compared to usual O₂ therapy.

Methods

Patients: 1,069 patients at 26 EDs in the UK.

Inclusion criteria: Adults aged >16y with a clinical or radiological diagnosis of acute cardiogenic pulmonary oedema, respiratory rate >20 breaths/min, and an arterial pH <7.35.

Exclusion criteria: Requirement for lifesaving or emergency intervention.

Groups: Concomitant therapies evenly assigned across groups:

- Standard O₂ therapy: supplemental O₂ via a variable-delivery O₂ mask with reservoir, titrated to peripheral O₂ saturations (O₂ sats) of 92%;
- CPAP: delivered via a full face mask, with supplemental O₂ supplied to maintain O₂ sats of 92%;
- NIPPV: delivered using a full face mask, with supplemental O₂ to maintain O₂ sats of 92%.

Outcome measures:

- Primary outcomes: comparison of NIV (NIPPV or CPAP) with standard O₂ therapy: 7-d mortality; comparison of NIPPV and CPAP: a composite endpoint of death or intubation within 7d;
- Secondary outcomes: patient-reported dyspnoea, intubation within 7d, length of hospital stay, admission to intensive care, 30-d mortality, change in physiological and biochemical parameters at 1h after commencement of treatment.

Results**Table 6.10** Summary of results

| | O ₂ treatment (<i>n</i> = 367) vs CPAP/NIPPV (<i>n</i> = 702) | CPAP (<i>n</i> = 346) vs NIPPV (<i>n</i> = 356) |
|-------------------------------|---|--|
| | OR (95% CI) | |
| Death or intubation within 7d | n/a | 0.94 (0.59–1.51) |
| Death within 7d | 0.97 (0.63–1.48) | 0.97 (0.58–1.61) |
| Death within 30d | 0.92 (0.64–1.31) | 0.98 (0.64–1.49) |
| Intubation within 7d | 1.05 (0.49–2.27) | 1.48 (0.6–3.67) |
| Admission to critical care | 1.21 (0.93–1.57) | 1.06 (0.78–1.43) |
| | Difference between means at 1h after treatment start (95% CI) | |
| Dyspnoea score | 0.7 (0.2–1.3) | –0.2 (–0.8 to 0.4) |
| Arterial pH | 0.03 (0.02–0.04) | –0.01 (–0.02 to 0.00) |

- Secondary outcomes (death, length of stay, intubation, intensive care admission, length of stay, physiological and biochemical changes) did not differ between patients receiving CPAP or NIPPV. (See Table 6.10.)

Discussion

Small, but meaningful, improvements in symptoms were found when using NIV, instead of standard O₂ therapy, for cardiogenic pulmonary oedema. However, there were no significant improvements in surrogate measures of disease severity or short-term mortality. No major differences in effectiveness were appreciable between the alternative NIV strategies of CPAP and NIPPV. The internal validity of the trial was good, with robust allocation concealment, complete follow-up of eligible patients, and low risk of information bias. Generalizability was also impressive, in contrast to preceding studies, with broad inclusion criteria and recruitment of 71% of eligible patients.

Problems

- A total of 87 patients were excluded after randomization, violating the intention-to-treat principle and risking selection bias;
- By necessity, clinicians could not be blinded to treatment allocation, and performance bias may have influenced the results.

DVT: clinical decision rule and D-dimer testing

Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis.

AUTHORS: Wells P, Anderson D, Rodger M et al.

REFERENCE: *N Engl J Med* (2003) **349**, 1227–35.

STUDY DESIGN: Multicentre, parallel-group randomized controlled equivalence trial.

EVIDENCE LEVEL: 1b.

Key message

Deep vein thrombosis (DVT) can be ruled out and ultrasound omitted in patients with a negative D-dimer result and judged unlikely to have a DVT, using the 2-level Wells clinical prediction score.

Impact

D-dimer measurement is now firmly established in the assessment of patients attending the ED with a suspected DVT, facilitating early hospital discharge and reducing the burden of limb ultrasound scans required.

Aims

The Wells score is a validated clinical prediction score for determining the pretest probability of DVT. The plasma level of D-dimer, a degradation product of cross-linked fibrin, is increased in the presence of venous thromboembolism (VTE). This study aimed to determine if combining the 2-level Wells score and D-dimer testing at presentation would safely rule out DVT and reduce ultrasound testing, compared to a strategy of using the clinical prediction score and routine ultrasound.

Methods

Patients: 1,096 outpatients from thrombosis units and EDs of five Canadian academic hospitals.

Inclusion criteria: Adult patients aged >18y with suspected lower limb DVT.

Main exclusion criteria: Suspicion of PE, prescribed anticoagulants, pregnancy.

Groups: All patients were first evaluated using the 2-level Wells clinical prediction score and classified as clinically likely or unlikely to have DVT.

- **Intervention group:** D-dimer testing was performed, in addition to assessment with the Wells clinical prediction score. Patients categorized as clinically unlikely to have DVT and whose D-dimer result was negative were discharged. All other patients received diagnostic ultrasound scanning. Patients judged to be clinically likely to have DVT, with positive D-dimer results but negative initial ultrasound, underwent a further ultrasound 1wk later;
- **Control group:** all patients received diagnostic ultrasound scans. For patients judged likely to have DVT, a second ultrasound was performed 1wk later, if the first was negative.

Outcome measures:

- Primary outcome: development of proximal DVT or PE within 3mo in patients in whom DVT had been initially excluded;
- Secondary outcome: mean number of lower limb ultrasound tests per patient.

Results**Table 6.11** Summary of results

| Outcome | Control group: ultrasound for all cases (<i>n</i> = 530) | Intervention group: D-dimer ± ultrasound (<i>n</i> = 566) | <i>p</i> |
|---|---|--|----------|
| VTE cases where DVT initially ruled out | 6 (1.4%, 95% CI 0.5–2.9) | 2 (0.4%, 95% CI 0.05–1.5) | 0.16 |
| Mean number of ultrasounds per patient | 1.34 | 0.78 | 0.008 |

- In patients clinically unlikely to have DVT, the NPV of the D-dimer test was 99.1 (95% CI 96.7–99.9), and the PPV was 14.1% (95% CI 7.95–22.6);
- In patients clinically likely to have DVT, the NPV of the D-dimer test was 89.0% (95% CI 80.7–94.6), and the PPV was 31.0% (95% CI 31.0–46.7). (See Table 6.11.)

Discussion

The 2-level Wells DVT clinical prediction score was used in this study, extending the original instrument to include patients with previous DVTs and reducing the number of risk categories to two (clinically likely or unlikely to have DVT). SimpliRED or IL-Test D-dimer assays were utilized, which may have slightly lower sensitivity and higher specificity than other D-dimer tests. If more sensitive enzyme-linked immunosorbent assays (ELISAs) are used, the risk of missed VTE should be similar or reduced, but it is possible that the reduction in the use of ultrasound imaging will be attenuated.

Problems

- An intention-to-treat analysis was not performed, with patients lost to follow-up excluded from calculations. Although missing outcomes were rare (1.9% control group, 0.7% D-dimer group), selection bias could conceivably have influenced effect estimates;
- A diagnostic gold standard was not performed on all patients, theoretically introducing a risk of verification bias into estimates of diagnostic accuracy. However, the 3-mo clinical follow-up would be expected to detect clinically significant episodes of VTE.

Endocrinology

- Introduction 180
- Hyperthyroidism: radioiodine 182
- Hyperthyroidism: methimazole 184
- Hypothyroidism: levothyroxine 186
- Primary hyperparathyroidism: medical treatment 188
- Primary hyperparathyroidism: surgical treatment 190
- Post-menopausal osteoporosis: bisphosphonates 192
- Paget's disease: bisphosphonates 194
- Male hypogonadism: testosterone replacement 196
- Acromegaly: octreotide 198
- Acromegaly: pegvisomant 200
- Hyperprolactinaemia: dopamine agonists 202

Introduction

One of the first properly described endocrine diseases arose in 1855, when Thomas Addison, a British scientist, reported a patient with Addison's disease. However, the modern concept of endocrinology, whereby a chemical messenger is secreted into the circulation to cause systemic effects, was born on 1 June 1889. On this date, Professor Charles-Edouard Brown-Séquard reported to a meeting in Paris that self-administration of aqueous extracts from guinea pig and dog testes improved physical strength, mental capacity, and sexual potency. In 1891, George Murray first treated a myxoedematous ♀ patient with thyroid extract, and, in 1894, Oliver and Schafer reported on epinephrine in the adrenal medulla. At the start of the twentieth century, endocrinology was still in its infancy. The medical term 'hormone' (derived from the Greek 'hormoa'—to excite) was only introduced by Ernest Starling in 1905 to describe chemical secretion from an endocrine gland. Since then, there has been tremendous progress in the field of endocrinology, as a result of advances in biochemistry, physiology, genetics, and molecular biology.

In 1909, Harvey Cushing successfully carried out the first modern-day endocrine surgery entailing the removal of a portion of the anterior pituitary gland in an acromegalic patient. Otto Loewi first identified neurohormones with the discovery of acetylcholine, for which he was subsequently awarded the Nobel Prize with Henry Dale in 1936. In 1971, Earl Sutherland was awarded the Nobel Prize for developing the concept of second messenger pathways, following work involving norepinephrine and cyclic adenosine monophosphate (AMP). Recently, advances in molecular biology, particularly sequencing of the human genome, have led to the unravelling of hormone receptor–post-receptor mechanisms. These discoveries have uncovered novel therapeutic targets for endocrine disease.

Hyperthyroidism: radioiodine

Long-term follow-up study of radioiodine treatment of hyperthyroidism.

AUTHORS: Metso S, Jaatinen P, Huhtala H *et al.*

REFERENCE: *Clin Endocrinol* (2004) **61**, 641–8.

STUDY DESIGN: Cohort.

EVIDENCE LEVEL: 2a.

Key message

The majority of patients with Graves' disease are rendered hypothyroid with radioiodine treatment.

Impact

Radioiodine therapy is an effective treatment for Graves' disease.

Aims

Hyperthyroidism is common, affecting ~2% of women and 0.2% of men. Untreated thyrotoxicosis can lead to CV and metabolic complications, which can be fatal. Radioactive iodine (RAI) has long been used to treat this condition and has been found to be safe and effective. The dose administered to give prompt control generally induces hypothyroidism, which can be treated with thyroxine to make the patient euthyroid. This study aimed to determine the long-term incidence of hypothyroidism after a fixed dose (259MBq) of RAI therapy and to evaluate whether clinical factors could predict the likelihood of hypothyroidism.

Methods

Patients: 2,043 patients at one university hospital in Finland.

Inclusion criteria:

- All patients with biochemical evidence of hyperthyroidism;
- Classified into Graves' disease, toxic multinodular goitre (MNG), or toxic adenoma.

Endpoints:

- Incidence of hypothyroidism;
- Number of radioiodine treatments needed to control hyperthyroidism;
- Clinical factors predicting the likelihood of hypothyroidism.

Follow-up: Started at the time of first RAI treatment. Study ran from 1965 to 2002 (study end) or till patient moved out of the area or death. Median F/U 9.8y.

Results

Table 7.1 Endpoint

| Endpoint | Graves' disease | Toxic MNG or adenoma |
|---------------------------------|-----------------|----------------------|
| 1y incidence of hypothyroidism | 24% | 4% |
| 10y incidence of hypothyroidism | 59% | 15% |
| 25y incidence of hypothyroidism | 82% | 32% |

Table 7.2 Summary of results

| Clinical factors | RR | | | |
|--|--------------------------------|-------|---|-------|
| | Graves' disease (n = 1,086) | p | Toxic MNG (n = 749) or adenoma (n = 208) | p |
| ♀ | 1.53 | <0.01 | 0.65 | 0.1 |
| Age at first RAI (RR/y) | 0.97 | <0.01 | 0.95 | <0.01 |
| Antithyroid drugs | 0.47 | <0.01 | 1.43 | 0.4 |
| Previous partial thyroidectomy | 1.63 | <0.01 | 1.59 | 0.03 |
| Remission after first radioiodine dose | 0.99 | 0.97 | 1.00 | 0.99 |

- Median time to development of hypothyroidism was 2y (minimum 1mo, maximum 25.4y). (See Tables 7.1 and 7.2.)

Discussion

The majority of patients with Graves' disease became hypothyroid by 25y following radioiodine therapy. However, this only happened in 32% of patients with MNG. Previous partial thyroidectomy and age at first RAI treatment were significantly associated with an increased risk of hypothyroidism. Graves' patients, unlike MNG patients, showed a decreased risk of hypothyroidism with previous antithyroid medication use, and an increased risk of hypothyroidism with ♀ gender. A total of 75% of patients were hypothyroid after a single dose of radioiodine, whereas 25% needed 2–6 doses, with no significant differences between the different aetiologies of hyperthyroidism.

Problems

- The majority of patients who participated had Graves' disease (53%), compared with toxic MNG (37%) and toxic adenoma (10%);
- The long-term CV and metabolic safety of radioiodine therapy was not investigated.

Hyperthyroidism: methimazole

Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine.

AUTHORS: Azizi F, Ataie L, Hedayati M *et al.*

REFERENCE: *Eur J Endocrinol* (2005) **152**, 695–701.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Hyperthyroidism is treated safely with long-term antithyroid medication.

Impact

Prolonged treatment with antithyroid medication is an alternative safe option to radioiodine therapy in patients with relapsed toxic goitre.

Aims

Patients with relapsed hyperthyroidism are usually treated with radioiodine therapy. This study aimed to investigate whether long-term antithyroid medication was a suitable alternative option to radioiodine therapy.

Methods

Patients: 67 patients at one centre in Iran.

Inclusion criteria:

- Age >40y;
- Hyperthyroidism due to diffuse toxic goitre;
- Recurrence of hyperthyroidism after initial treatment with antithyroid drugs for 1y.

Groups:

- Methimazole ($n = 26$);
- Radioiodine ($n = 41$).

Endpoints:

- Thyroid function tests;
- Antithyroperoxidase antibodies;
- Cholesterol;
- Goitre rate;
- Bone mineral density (BMD);
- Serious adverse events;
- Cost of treatment.

Follow-up: Median F/U 10.2y.

Results

Table 7.3 Summary of results

| Endpoint | Methimazole | Radioiodine | p |
|--------------------------------------|--------------|--------------|--------|
| Free T ₄ (ng/dL) | 1.5590.50 | 1.6390.44 | ns |
| Free T ₃ (pg/mL) | 3.66 ± 0.72 | 3.44 ± 0.77 | ns |
| TSH (mU/L) | 1.7 ± 1.7 | 4.3 ± 6.4 | ns |
| Antithyroperoxidase antibody (IU/mL) | 244 ± 277 | 45 ± 81 | <0.05 |
| Cholesterol (mg/dL) | 190 ± 47 | 224 ± 46 | <0.01 |
| LDL cholesterol (mg/dL) | 99 ± 41 | 132 ± 46 | <0.01 |
| Total goitre rate (%) | 50 | 25 | <0.05 |
| Total BMD at the hip (Z score) | -0.31 ± 0.84 | -0.54 ± 0.94 | ns |
| Total BMD at the radius (Z score) | -1.41 ± 1.20 | -1.70 ± 1.11 | ns |
| Serious adverse events | 0 | 0 | ns |
| Cost of management (US\$) | 631 ± 32 | 691 ± 36 | <0.001 |

LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.

Discussion

This study demonstrated that, in patients with diffuse toxic goitre, long-term methimazole was a safe and cost-effective alternative to radioiodine. Compared with radioiodine, 10y of methimazole treatment resulted in no significant difference in thyroid function tests or BMD, and a higher goitre rate and level of antithyroperoxidase antibodies, but a reduction in total and LDL cholesterol. In the UK, the treatment of choice for patients with relapsed hyperthyroidism remains radioiodine therapy, but long-term antithyroid medication may be considered a safe and cost-effective alternative. (See Table 7.3.)

Problems

- The study was limited to patients >40y of age with diffuse toxic goitre and did not include the more prevalent Graves' patients who make up an important group of thyroid patients seen in the endocrine clinic;
- There was a high dropout rate of 8% which may have biased the results, and the numbers in each group were small, thus limiting the power of the study;
- The cost comparison was based on each group being followed up on a 6-monthly basis, but, in clinical practice, the methimazole group may have to be followed up more frequently to alter the dose of treatment. This may also be a significant factor in adverse compliance outside the setting of a controlled study.

Hypothyroidism: levothyroxine

The starting dose of levothyroxine in primary hypothyroidism treatment.

AUTHORS: Roos A, Linn-Rasker S, van Domburg R et al.

REFERENCE: *Arch Intern Med* (2005) **165**, 1714–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A full starting replacement dose of levothyroxine in patients with 1° hypothyroidism (without known cardiac disease) is a safe treatment option.

Impact

This was the first prospective study to investigate the safety and efficacy of initial levothyroxine starting doses in patients with 1° hypothyroidism.

Aims

Hypothyroidism is common, particularly in women. It is most often due to autoimmune thyroiditis. Suggested starting doses for replacement therapy vary considerably. This study aimed to investigate the safety of higher initial replacement doses of levothyroxine.

Methods

Patients: 50 patients at one centre in the Netherlands.

Inclusion criteria:

- Untreated 1° autoimmune hypothyroidism;
- Serum thyrotropin >4.2mIU/L, free T₄ <10pmol/L.

Exclusion criteria:

- History of cardiac disease;
- Patients on cardiac medications.

Groups:

- Full starting dose: levothyroxine (1.6 micrograms/kg) (*n* = 25);
- Low starting dose: levothyroxine (25 micrograms, dose increased every 4wk) (*n* = 25).

Endpoints:

- Cardiac adverse events;
- Thyroid function tests;
- Lipids;
- Exercise performance (bicycle ergometer);
- QoL scores.

Follow-up: Up to 48wk. Review every 4wk (first 24wk of treatment), then every 12wk. Included clinical symptom score, cardiac assessment, and patient questionnaires.

Results

Table 7.4 Summary of results

| Endpoint | (Full dose) Levothyroxine 1.6 micrograms/kg | (Low dose) Levothyroxine 25 micrograms | <i>p</i> |
|---|---|--|--------------|
| Time to normalization of thyrotropin levels | 4wk | 16wk | – |
| 4wk median thyrotropin levels (mIU/L) | 4.2 | 26.7 | 0.005 |
| 4wk median free T ₄ levels (pmol/L) | 19 | 12 | <0.01 |
| Significant change in cholesterol levels (number of patients) | 0 | 0 | Not reported |
| Cardiac symptoms/ events (number of patients) | 0 | 0 | Not reported |
| Change in exercise performance (%) | 10 | 0 | <0.001 |
| Change in QoL score (%) | +19 | +26 | Not reported |

Discussion

This study demonstrated that a 1.6 micrograms/kg dose of levothyroxine was safe in patients without known cardiac disease. Greater increases were observed in 4-wk free T₄ levels and exercise performance in the higher-dose levothyroxine group, compared with the group starting on the lower dose of 25 micrograms. There were no significant changes in QoL scores or cholesterol levels. The authors postulated that the high-dose regime might be more cost-effective and convenient, thus improving compliance. However, this conclusion was not formally evaluated in this study. (See Table 7.4.)

Problems

- Levothyroxine was given in a liquid formulation, rather than the more widely used tablet preparation;
- Only 25 patients in each group were studied, which may make the study insufficiently powered to arrive at meaningful conclusions.
- The mean patient age was 47y. Even though some elderly patients were included, the application of these results to older populations needs to be done with caution;
- This study did not address the safe starting dose of levothyroxine in patients with cardiac disease.

Primary hyperparathyroidism: medical treatment

Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism.

AUTHORS: Peacock M, Bilezikian J, Klassen P et al.

REFERENCE: *J Clin Endocrinol Metab* (2005) **90**, 135–41.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Calcium and parathyroid hormone (PTH) levels are rapidly and effectively reduced with cinacalcet therapy.

Impact

Medical treatment with cinacalcet can be considered as a non-surgical option for the maintenance of normocalcaemia in patients with mild to moderate 1° hyperparathyroidism.

Aims

There are limited therapeutic alternatives for patients who are either not cured by, or have contraindications to, parathyroidectomy. This trial was designed to see whether the calcimimetic cinacalcet could safely reduce calcium and PTH levels in this group. Additionally, it aimed to explore the metabolic effects of therapy on bone structure.

Methods

Patients: 78 patients from 18 centres in the USA.

Inclusion criteria:

- Serum calcium level $>2.57\text{mmol/L}$ and $<3.12\text{mmol/L}$;
- PTH level $>4.73\text{pmol/L}$.

Exclusion criteria:

- Creatinine clearance $<50\text{mL/min}$;
- Treatment with bisphosphonates or fluoride;
- Familial hypocalciuric hypercalcaemia;
- Patients who required drugs that are metabolized by cytochrome P450.

Groups:

- Cinacalcet (30mg bd, increased up to 50mg bd, if needed) ($n = 40$);
- Placebo ($n = 38$).

Primary endpoint: Serum calcium $\leq 2.57\text{mmol/L}$ and a reduction from baseline of $\geq 0.12\text{mmol/L}$.

Secondary endpoints:

- Plasma PTH, serum and urine biochemistry, biochemical measures of bone turnover (bone-specific alkaline phosphatase (BALP), N-telopeptide (NTx));
- Adverse events.

Follow-up: Total F/U 52wk. Included clinical/biochemical measurement and modification of dosage, if required.

Results**Table 7.5** Summary of results

| Primary endpoint | Cinacalcet | Placebo | <i>p</i> |
|------------------------------------|---|---|----------|
| Calcium ≤ 2.57 mmol/L | 73% | 5% | <0.001 |
| Secondary endpoint | | | |
| PTH change | −7.6% | +7.7% | <0.01 |
| Serum phosphorus | +18.5% | −3.6% | <0.001 |
| Calcium/creatinine | −38.5% | +12.0% | <0.001 |
| Serum BALP | +35.3% | +4.4% | <0.05 |
| Serum NTx | +27.8% | No change | <0.05 |
| Urine NTx/creatinine | +60.4% | −4.7% | <0.001 |
| Tubular reabsorption of calcium | +5.7% | No change | <0.001 |
| Tubular reabsorption of phosphorus | +29.6% | No change | <0.001 |
| BMD (Z score) change | Lumbar: 0.00; femur: −0.01; radius: −0.05 | Lumbar: 0.03; femur: −0.02; radius: −0.01 | ns |

Discussion

This trial demonstrated the effectiveness of cinacalcet in reducing serum calcium levels, reducing PTH levels, and increasing bone resorption and formation markers. In 90% of patients, the dose needed to maintain normocalcaemia was 30mg bd. Importantly, the trial found cinacalcet to be well tolerated, with non-significant adverse effects. Two-thirds of patients not previously cured by parathyroidectomy reached the primary endpoint with cinacalcet. (See Table 7.5.)

Problems

- The trial was of only 52-wk duration, so the long-term complications of 1° hyperparathyroidism were not analysed. No data were collected on hard endpoints such as mortality, skeletal fractures, renal stones, CV disease, or GI manifestations;
- The trial was limited to patients with mild to moderate hyperparathyroidism, so patients with severe hypercalcaemia or asymptomatic hyperparathyroidism were not analysed;
- The trial was not designed to look at the cost benefit of cinacalcet vs parathyroidectomy.

Primary hyperparathyroidism: surgical treatment

Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism.

AUTHORS: Rao DS, Phillips E, Divine G *et al.*

REFERENCE: *J Clin Endocrinol Metab* (2004) **89**, 5415–22.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Parathyroidectomy in patients with mild asymptomatic hyperparathyroidism is beneficial in improving BMD, QoL, and psychological function, compared with no surgery.

Impact

This was the first RCT to have been conducted to investigate the benefits of surgery vs no surgery in asymptomatic patients with 1° hyperparathyroidism.

Aims

Parathyroidectomy is well recognized as the most appropriate treatment of symptomatic hyperparathyroidism. However, surgery in the absence of symptoms remains controversial. This trial aimed to evaluate the benefits of parathyroidectomy vs no surgery in patients with mild asymptomatic hyperparathyroidism.

Methods

Patients: 53 patients at one centre in the USA.

Inclusion criteria:

- Age 50–75y;
- Corrected calcium levels 10.1–11.5mg/dL (2.52–2.87mmol/L);
- PTH >20pg/mL (20 ng/L);
- Creatinine <1.5mg/dL (133micromol/L);
- Forearm BMD within 2SD adjusted for age, sex, and race (Z scores);
- Absence of symptoms and complications due to hypercalcaemia or excess PTH levels.

Exclusion criteria:

- Familial hyperparathyroidism;
- Previous neck surgery;
- Active thyroid disease requiring surgical intervention;
- Non-traumatic vertebral or hip fractures;
- Nephrolithiasis within the past 2y;
- Women within 5y of the menopause;
- Medications known to affect bone and mineral metabolism;
- Adverse echo findings (that would preclude surgery).

Groups: Parathyroidectomy ($n = 25$); no surgery ($n = 28$).

Endpoints: BMD and bone biochemistry; QoL.

Follow-up: Included clinical/biochemical assessment, and QoL/psychosocial well-being questionnaires. Median F/U 42mo.

Results

Table 7.6 Percentage change in BMD per year

| % change in BMD/y | Surgery | No surgery | <i>p</i> |
|-------------------|---------|------------|--------------|
| Spine | 1.2 | 0.5 | Not reported |
| Femoral neck | 0.4 | -0.4 | 0.01 |
| Total hip | 0.3 | -0.6 | 0.001 |
| Forearm | 0.4 | 0.2 | Not reported |

Table 7.7 Summary of results

| | Before surgery | After surgery | <i>p</i> |
|----------------------------------|------------------|-----------------|--------------|
| Calcium (mg/dL) | 10.41 ± 0.51 | 9.22 ± 0.42 | <0.001 |
| PTH (pg/mL) | 87 ± 27 | 39 ± 28 | <0.001 |
| Urine calcium (mg/d) | 252 ± 135 | 147 ± 86 | <0.001 |
| Urine calcium/creatinine (mg/mg) | 0.15 ± 0.08 | 0.11 ± 0.14 | Not reported |

- Biochemical parameters were unchanged in patients without surgery;
- Social ($p = 0.007$) and emotional function ($p = 0.012$) was better in the parathyroidectomy group, compared with the non-surgery group;
- Anxiety ($p = 0.003$) and phobia ($p = 0.024$) declined in the parathyroidectomy group, compared with the non-surgery group. (See Tables 7.6 and 7.7.)

Discussion

The ideal treatment of asymptomatic hyperparathyroid patients has been controversial. This was the first RCT to evaluate this question. There were benefits seen in BMD (only at the femoral neck and total hip), QoL, and psychological function in the parathyroidectomy group. However, these slight benefits need to be weighed up against the complications of parathyroid surgery.

Problems

- The surgical group had a higher mean age;
- Patients aged <50y, in whom there is a high prevalence of hypercalcaemic complications, were not included;
- The numbers in this study were small, and the F/U period was too short to assess morbidity and mortality data.

Post-menopausal osteoporosis: bisphosphonates

FIT (Fracture Intervention Trial): Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures.

AUTHORS: Black D, Cummings S, Karpf D et al.

REFERENCE: *Lancet* (1996) **348**, 1535–41.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Post-menopausal women with low bone mass and a previous history of vertebral fractures have a lower incidence of fractures with alendronate therapy.

Impact

Alendronate is the most commonly used therapy in post-menopausal osteoporosis.

Aims

In women, the risk of osteoporosis increases after the menopause. Several treatments have been shown to have efficacy in increasing bone mass, including bisphosphonates. This trial aimed to evaluate the effect of the bisphosphonate alendronate on the clinical and radiological incidence of vertebral and non-vertebral fractures in post-menopausal women with a previous history of vertebral fractures.

Methods

Patients: 2,027 women from 11 centres in the USA.

Inclusion criteria:

- ≥ 2 y post-menopause;
- Femoral neck BMD of $\leq 0.68\text{g/cm}^2$;
- At least one previous vertebral fracture at recruitment.

Exclusion criteria:

- Peptic ulcer disease or dyspepsia requiring treatment;
- Abnormal renal function;
- Major medical problems likely to stop participation for 3y.
- Severe malabsorption syndrome;
- Uncontrolled HTN (SBP $> 210\text{mmHg}$, DBP $> 105\text{mmHg}$);
- MI during previous 6mo or unstable angina;
- Abnormal thyroid or parathyroid function;
- Previous bisphosphonates or sodium fluoride use.

Groups: Alendronate ($n = 1,022$); placebo ($n = 1,005$).

Primary endpoints: New morphometric vertebral fractures.

Secondary endpoints: Any clinical fracture, bone mass, adverse effects (in particular GI).

Follow-up: Mean F/U 2.9y. Included BMD (at 1, 2, and 3y) and radiographs (at 2 and 3y).

Results

Table 7.8 Summary of results

| Endpoint | Alendronate | Placebo | HR (95% CI) |
|-------------------------------------|-------------|-------------|---------------------|
| ≥1 morphometric vertebral fractures | 78 (8.0%) | 145 (15.0%) | RR 0.53 (0.41–0.68) |
| Clinical vertebral fractures | 23 (2.3%) | 50 (5.0%) | 0.45 (0.27–0.72) |
| Any clinical fracture | 139 (13.6%) | 182 (18.2%) | 0.72 (0.58–0.90) |
| Any non-vertebral fracture | 22 (11.9%) | 148 (14.7%) | 0.80 (0.63–1.01) |
| Hip fracture | 11 (1.1%) | 22 (2.2%) | 0.49 (0.23–0.99) |
| Wrist fracture | 22 (2.2%) | 41 (4.1%) | 0.52 (0.31–0.87) |
| Upper GI disturbance | 422 (41.3%) | 402 (40.0%) | $p = 0.67$ |

Table 7.9 Summary of results (continued)

| Endpoint | Alendronate vs placebo | p |
|------------------------|------------------------|--------|
| Femoral bone mass | 4.1% | <0.001 |
| Total hip bone mass | 4.7% | <0.001 |
| Lumbar spine bone mass | 6.2% | <0.001 |

Discussion

Post-menopausal women with low bone mass and previous vertebral fractures had a lower incidence of clinical and radiological fractures. The alendronate group had 47% fewer radiographic vertebral fractures, and 55% fewer clinical vertebral fractures. No significant differences in adverse GI events were seen. (See Tables 7.8 and 7.9.)

Problems

- This arm of the FIT trial did not study fracture risk in women without a pre-existing history of vertebral fractures. Additionally, only women with low BMD were included;
- The ethnic diversity was limited, 97% of patients being Caucasian;
- There were no long-term data, the trial being limited to 3y;
- The cost–benefit ratio of alendronate treatment was not assessed.

Paget's disease: bisphosphonates

Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease.

AUTHORS: Reid I, Miller P, Lyles K et al.

REFERENCE: *N Engl J Med* (2005) 353, 898–908.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A single infusion of zoledronic acid is a rapid and effective treatment regime for patients with Paget's disease.

Impact

Bisphosphonate therapy is the first-line treatment for patients with Paget's disease, and, as a result of this study, zoledronic acid is considered the most effective way to achieve sustained remission.

Aims

Paget's disease is characterized by increased bone turnover, often resulting in bone pain. Bisphosphonates can suppress this process. This study aimed to compare the effects of two different bisphosphonates—IV zoledronic acid and oral risedronate—on biochemical markers of Paget's disease activity and QoL measures.

Methods

Patients: 357 patients from 76 centres in ten countries.

Inclusion criteria:

- Age >30y;
- Radiological evidence of Paget's disease.

Exclusion criteria:

- Serum vitamin D <37nmol/L;
- 1° hyperparathyroidism, hepatic or renal disease;
- History of uveitis, iritis, upper GI disorders, diabetic nephropathy, or retinopathy;
- Paget's disease therapy in preceding 180d.

Groups:

- Zoledronic acid 5mg IV ($n = 182$);
- Risedronate 30mg orally (PO) ($n = 175$).

Primary endpoints: Alkaline phosphatase (ALP) normalization or reduction of $\geq 75\%$ of ALP excess (from midpoint of reference range).

Secondary endpoints:

- Biochemical markers of bone resorption and formation;
- QoL (Medical Outcomes Study 36-item Short-Form General Health Survey (SF36));
- Adverse events;
- Loss of primary endpoint at median 190d after study.

Follow-up: 6mo.

Results

Table 7.10 Summary of results

| Endpoint | Zoledronic acid | Risedronate | p |
|---|-----------------|-------------|--------|
| Primary endpoint | 96% | 74.3% | <0.001 |
| Mean time to primary endpoint | 64d | 89d | <0.001 |
| ALP normalization | 88.6% | 57.9% | <0.001 |
| Loss of primary endpoint at median 190d after study | 0.9% | 25.6% | <0.001 |
| Adverse events (1–3d) | 53.7% | 25% | <0.01 |
| Adverse events (after 3d) | 66.1% | 73.3% | 0.2 |

Secondary endpoints:

- Bone formation marker: N-terminal propeptide of type I collagen showed a significant decrease in both groups from baseline, with the response being greater in the zoledronic acid group;
- Bone resorption markers: β C-telopeptide of type I collagen and ratio of urinary α C-telopeptide of type I collagen to creatinine showed greater reductions in the zoledronic acid group;
- SF36 (QoL): the zoledronic acid group showed a significant increase from baseline at 3 and 6mo, and was significantly greater than the risedronate group at 3mo. (See Table 7.10.)

Discussion

Treatment with zoledronic acid resulted in a greater significant effect in suppressing Paget's disease activity, which was more rapid, sustained, and associated with improvements in QoL. In the zoledronic acid group, there was twice the number of adverse events in the first 3d, mostly due to influenza-like symptoms (which mainly resolved after 4d). After 3d, the rate of adverse events was similar in the two groups.

Problems

- The study was only for 6mo, so longer-term data are needed to evaluate treatment response and adverse events;
- The majority of patients were 4 (68%).

Male hypogonadism: testosterone replacement

A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function.

AUTHORS: McNicholas T, Dean J, Mulder H et al.

REFERENCE: *BJU Int* (2003) **91**, 69–74.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Testosterone gel preparation is an effective alternative route for testosterone replacement in hypogonadal 4.

Impact

With the recent availability of testosterone gel preparations, patients have been offered an alternative choice for testosterone replacement, which is more tolerable than traditional transdermal testosterone patches.

Aims

Declining testosterone levels in men can lead to altered mood and sexual function. Testosterone replacement through transdermal patches, oral formulations, or IM injections were all previously used. However, all had associated problems (e.g. pain, inconvenience). Although patches were the most convenient for patients, a gel preparation had been proposed to provide more consistent therapeutic levels of testosterone. This study aimed to compare the effects of testosterone gel (Testim™) with the more established transdermal testosterone patch (Andropatch®) as a way of administering testosterone replacement in hypogonadal patients.

Methods

Patients: 208 patients from 29 European centres.

Inclusion criteria:

- Hypogonadal men (morning testosterone <10.4nmol/L);
- ≥1 symptom of hypogonadism.

Groups:

- Testim™ 50 (containing 5mg of testosterone) (*n* = 68);
- Testim™ 100 (containing 10mg of testosterone) (*n* = 72);
- Testosterone patch (containing 5mg of testosterone) (*n* = 68).

Measurements:

- Androgen levels;
- Body composition (i.e. lean body mass, fat mass, % of body fat, and BMD of L1–L4 sections of the lumbar spine by dual-energy X-ray absorptiometry (DEXA));
- Sexual function and mood;
- Adverse events.

Follow-up: Clinical assessment (including sexual function and mood questionnaires) at 30, 60, and 90d.

Results**Table 7.11** Summary of results

| Measurement change | Testim™ 50 | Testim™ 100 | Andropatch® |
|---------------------------------|------------|-------------|-------------|
| Testosterone (nmol/L) | 6.54 | 12.41 | 3.82 |
| DHT (nmol/L) | 0.91 | 1.39 | 0.03 |
| Free testosterone (pmol/L) | 22.07 | 47.83 | 15.74 |
| Spontaneous erections (mean/wk) | 0.6 | 0.5 | 0.3 |
| Motivation (mean/wk) | 0.4 | 0.4 | 0.5 |
| Desire (mean/d) | 0.8 | 0.7 | 0.5 |
| Performance (mean/wk) | 0.3 | 0.4 | 0.3 |
| Lean body mass | 0.9 | 1.5 | 1.0 |
| Fat mass | −0.1 | −0.2 | −0.1 |
| % fat | −0.4 | −0.7 | −0.3 |
| Adverse events | 35% | 29% | 63% |

DHT, dihydrotestosterone.

Discussion

Compared with the transdermal patch, testosterone delivered in a gel preparation was more effective at normalizing androgen levels in a dose-dependent manner. Additionally, there was a significant improvement in sexual function, mood, and body composition. The transdermal patch had more adverse effects, mainly due to skin irritation, which resulted in a greater discontinuation rate. This is an important factor, as testosterone replacement in hypogonadal patients is a long-term therapy. (See Table 7.11.)

Problems

- No comparison was made between other testosterone replacement therapies, in particular the commoner testosterone injections;
- The majority of patients had 2°, rather than 1°, hypogonadism.

Acromegaly: octreotide

Primary treatment of acromegaly with octreotide LAR: prospective study of its efficacy in the control of disease activity and tumour shrinkage.

AUTHORS: Cozzi R, Montini M, Attanasio R et al.

REFERENCE: *J Clin Endocrinol Metab* (2006) **91**, 1397–403.

STUDY DESIGN: Cohort study.

EVIDENCE LEVEL: 2b.

Key message

Long-acting repeatable (LAR) octreotide is an effective 1° therapy in acromegalic patients with large or invasive adenomas and high growth hormone (GH) levels.

Impact

LAR octreotide is considered the first treatment option for acromegalic patients with large invasive adenomas who are poor surgical candidates.

Aims

While surgical management is the treatment of choice for acromegaly, in some patients, this is not an option, and so medical therapy is required. This trial aimed to study the effect of the somatostatin analogue LAR octreotide as 1° treatment for patients with acromegaly.

Methods

Patients: 67 patients (72% macroadenomas) at one centre in Italy.

Inclusion criteria:

- Clinical symptoms and signs of acromegaly;
- Elevated GH not suppressed after an oral glucose tolerance test;
- High age-adjusted insulin-like growth factor-1 (IGF-1) levels;
- MRI showing macroadenoma or invasive microadenoma;
- No previous neurosurgery or radiotherapy.

Exclusion criteria:

- Intrasellar microadenoma (except patients refusing, or unable to have, neurosurgery);
- Ophthalmological or neurological involvement;
- Hepatic or renal disease.

Endpoints:

- GH level <2.5 micrograms/L;
- Normal age-matched IGF-1 level;
- Tumour shrinkage on MRI.

Follow-up: Up to 48mo. Assessment at 3- to 6-monthly intervals during the first year, then annually thereafter. MRI before start of treatment, and at 6 and 12mo.

Results

Table 7.12 Summary of results

| | |
|--|-------------|
| GH level <2.5 micrograms/L (% of patients) | 68.7 |
| Percentage decrease in GH | 81.5 ± 21.7 |
| Normal age-matched IGF-1 level (% of patients) | 70.1 |
| Percentage decrease in IGF-1 | 59 ± 27 |
| Tumour decreased in size (% of patients) | 82.1 |
| Percentage tumour decrease from baseline | 62 ± 31% |
| Tumour shrinkage >75% (% of patients) | 44 |

Discussion

LAR octreotide therapy in treatment-naïve patients with acromegaly resulted in normalization of GH and IGF-1 levels in over two-thirds of patients. This occurred, regardless of the baseline levels of GH or IGF-1, although the greatest normalization occurred in those patients with higher baseline values. Tumour shrinkage occurred more frequently with macroadenomas, compared with microadenomas. (See Table 7.12.)

Problems

- A total of 49% of patients initially having LAR octreotide decided to change to an alternative treatment for their acromegaly (surgery or addition of lanreotide or cabergoline);
- The majority of patients had macroadenomas, and the study did not include acromegalic patients with only intrasellar adenomas;
- There was no control group in the trial.

Acromegaly: pegvisomant

Long-term treatment of acromegaly with pegvisomant, a growth hormone receptor antagonist.

AUTHORS: van der Lely A, Hutson R, Trainer P *et al.*

REFERENCE: *Lancet* (2001) **358**, 1754–9.

STUDY DESIGN: Cohort study.

EVIDENCE LEVEL: 2b.

Key message

Pegvisomant reduces IGF-1, fasting insulin, and fasting glucose levels in patients with acromegaly.

Impact

Pegvisomant is the first highly selective GH receptor antagonist that has been shown to be an effective medical treatment option for acromegalic patients.

Aims

Traditional management of acromegaly involves either surgery or medication (dopamine agonists/somatostatin analogues). This trial aimed to assess the efficacy of a novel drug SC pegvisomant (a GH receptor agonist) in patients with acromegaly.

Methods

Patients: 160 patients at multiple international centres.

Inclusion criteria:

- Age >18y;
- IGF-1 levels ≥ 1.3 times the upper end of age-adjusted normal range;
- Somatostatin analogues discontinued for ≥ 2 wk;
- Dopamine agonists discontinued for ≥ 5 wk.

Endpoints:

- Pituitary tumour volume change assessed by MRI;
- GH levels;
- IGF-1 levels;
- Fasting insulin levels;
- Fasting glucose levels.

Follow-up: 425d.

Results

Table 7.13 Summary of results

| Endpoint | 6-mo cohort (n = 131) | 12-mo cohort (n = 90) | 18-mo cohort (n = 39) | p |
|---------------------------------------|--------------------------|--------------------------|--------------------------|--------|
| Decrease in IGF-1 (micrograms/L) | 467 | 526 | 523 | <0.001 |
| Increase in GH (micrograms /L) | 12.5 | 12.5 | 14.2 | <0.001 |
| Decrease in fasting insulin (mU/L) | 7.2 | 10.6 | 10.9 | 0.039 |
| Fasting glucose(mg/L) | 191 | 147 | 80 | 0.013 |

- A total of 97% of patients treated for >52wk had a normal IGF-1 level;
- A total of 16.9% developed antibodies to GH (but no tachyphylaxis occurred) (see Table 7.13);
- Mean tumour volume decreased by 0.033cm³ at 11.46mo ($p = 0.353$, ns).

Discussion

This study demonstrated a significant reduction in IGF-1, insulin, and glucose levels with pegvisomant therapy. GH levels rose in the first 6mo and remained stable thereafter. The mechanism by which this happened was unclear. Serum GH is not a good marker of acromegalic activity in patients treated with pegvisomant. The mean tumour volume did not decrease significantly.

Problems

- A total of 18.8% of patients withdrew from the study;
- The effect of pegvisomant on symptoms and QoL was not assessed;
- Long-term F/U is needed to exclude an increase in tumour volume (Nelson's syndrome-like effect—rapid pituitary tumour enlargement occurring post-bilateral adrenalectomy);
- The trial did not study the efficacy of pegvisomant compared with other forms of medical therapy for acromegaly, including dopamine agonists and somatostatin analogues.

Hyperprolactinaemia: dopamine agonists

A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea.

AUTHORS: Webster J, Piscitelli G, Polli A *et al.*

REFERENCE: *N Engl J Med* (1994) 331, 904–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with hyperprolactinaemic amenorrhoea, cabergoline therapy is more efficacious and tolerable than bromocriptine.

Impact

The dopamine agonist cabergoline is considered first-line treatment for patients with hyperprolactinaemia.

Aims

Dopamine agonists are the treatment of choice for hyperprolactinaemia. This trial aimed to compare cabergoline, a newer long-acting dopamine agonist, with the former gold standard bromocriptine.

Methods

Patients: 459 patients from multiple international centres (279 microprolactinomas, three macroprolactinomas, one craniopharyngioma, 167 idiopathic hyperprolactinaemias, nine empty sellae).

Inclusion criteria:

- ♀ with amenorrhoea >3mo;
- Serum prolactin level at least twice the upper limit of normal;
- ≥4wk discontinuation of previous prolactin therapy.

Exclusion criteria:

- Any previous SEs to either one of the dopamine agonists;
- Any disorder preventing normal menstruation after normalization of prolactin;
- Hyperprolactinaemia due to polycystic ovary syndrome (PCOS), thyroid or adrenal disorders, renal or hepatic disease.

Groups:

- Cabergoline (0.5–1.0mg twice weekly) (*n* = 223);
- Bromocriptine (2.5–5.0mg twice weekly) (*n* = 236).

Endpoints:

- Occurrence of menses and ovulation;
- Serum prolactin levels;
- Adverse events.

Follow-up: Clinical assessment (including checking SEs) and serum prolactin measurements at baseline, and at 2, 4, 6, 8, 12, 14, 16, 20, and 24wk after initiation of therapy.

Results

Table 7.14 Summary of results

| Endpoint | Cabergoline | Bromocriptine | <i>p</i> |
|-------------------------------|-------------|---------------|----------|
| Normoprolactinaemia | 83% | 59% | <0.001 |
| Ovulatory cycles or pregnancy | 72% | 52% | <0.001 |
| Persistence of amenorrhoea | 7% | 16% | ns |
| Adverse events | 68% | 78% | 0.03 |
| Drug intolerance | 3% | 12% | <0.001 |

Discussion

This study demonstrated cabergoline to be more effective at normalizing prolactin levels and restoring normal menstruation and ovulation, compared with bromocriptine. Adverse events were significantly fewer, and tolerability significantly better, in the cabergoline group. (See Table 7.14.)

Problems

- Treatment was only double-blinded for the first 8wk, then continued open-labelled. The authors state that most SEs occurred within the first few weeks, though continuing the double-blind design would have been a better study design;
- Only 72% in the bromocriptine group, and 83% in the cabergoline group, completed the 24-wk study.

Gastroenterology

Introduction 206

Colorectal cancer: once-only flexible sigmoidoscopy screening 208

Gastric cancer: *Helicobacter pylori* eradication 210

Peptic ulcer disease: *Helicobacter pylori* eradication 212

Peptic ulcer disease: managing antiplatelet bleeding risk 214

Peptic ulcer disease: endoscopic control of bleeding 216

Upper gastrointestinal bleeding: red cell transfusion 218

Upper gastrointestinal bleeding: intravenous proton pump inhibitor 220

Variceal bleeding: primary prevention 222

Gastrointestinal bleeding with cirrhosis: antibiotic prophylaxis 224

Alcoholic hepatitis: corticosteroids 226

Alcoholic hepatitis: combination therapy 228

Ascites: fluid replacement following paracentesis 230

Ulcerative colitis: ciclosporin 232

Crohn's disease: infliximab 234

Hepatitis C: peginterferon and ribavirin 236

Chronic hepatitis C: triple therapy 238

Introduction

'One good set of bowels is more important than any amount of brain' were the wise words that inspired gastroenterologists for centuries. Fittingly, an earnest gastroenterologist spent good time on ward rounds stool-gazing. The arrival of flexible endoscopy brought glamour to the specialty, which had long been monopolized by cardiology. Despite being sneered upon by intellectuals as 'just a tool', endoscopy continues to challenge surgery and radiology, driving both of these specialties to advances in laparoscopic techniques and newer sophisticated imaging modalities. The discovery of *Helicobacter pylori* has made surgery for 'peptic ulcers' history. Refinements in endoscopic haemostatic techniques are even raising concerns that surgical trainees may not get sufficient experience in dealing with acute GI bleeding.

Over the last two decades, there has been a marked improvement in the quality of study design and statistical rigour. However, the complexity of gastroenterological problems has limited the size of the studies which still do not compare with those performed in cardiology. Biological therapy in inflammatory bowel disease has been a therapeutic landmark in therapeutics in gastroenterology, not only for increasing the sophistication in study design, but also for stimulating debate on fundamental goals of therapy. In hepatology, antiviral therapy has established large and robust multinational RCTs. Interventions in hepatology are now judged by their effect on hard clinical endpoints, including long-term survival.

Clinical gastroenterology has matured into a specialty that challenges both the intellect and dexterity.

Colorectal cancer: once-only flexible sigmoidoscopy screening

Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial.

AUTHORS: Atkin W, Edwards R, Kralj-Hans I *et al.*

REFERENCE: *Lancet* (2010) 375, 1624–33.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Once-only flexible sigmoidoscopy screening in patients aged between 55 and 64y significantly reduces the incidence of, and mortality from, colorectal cancer. It is cost-effective and acceptable to patients, making it a suitable method for population screening.

Impact

Population screening in the UK currently relies on faecal occult blood testing. However, as a result of this study, the UK's NHS are piloting a flexible sigmoidoscopy screening programme from March 2013 for people in England aged over 55y.

Aims

CRC is the 3rd commonest cancer worldwide, accounting for substantial morbidity and mortality. This study aimed to examine the efficacy and duration of effect of: (1) a single flexible sigmoidoscopy (FS) test offered to patients aged between 55 and 64; (2) removal of <10mm polyps during screening; and (3) colonoscopy for only in those with high-risk adenomas.

Methods

Patients: 170,432 patients from 14 UK centres.

Inclusion criteria:

- Men and women aged between 55 and 64y;
- Registered with participating GPs.

Exclusion criteria:

- History of CRC, adenomas, or inflammatory bowel disease;
- Inability to provide informed consent;
- Life expectancy <5y;
- Sigmoidoscopy/colonoscopy in the last 3y.

Groups: Randomized in a 1:2 ratio:

- Control group ($n = 113,195$): not contacted;
- Intervention group ($n = 57,237$): offered FS screening.

Primary endpoint: CRC incidence and mortality.

Secondary endpoints:

- All-cause mortality;
- Incidence of distal and proximal CRC;
- Mortality due to non-CRC causes.

Follow up: 11y.

Results

Table 8.1 Summary of results

| Primary endpoints (per 100,000 patient years) | Control group | Intervention group | Reduction (%) | HR |
|---|------------------|-----------------------|------------------|------------------|
| CRC incidence | 149 | 100 | 33 | 0.67 (0.60–0.76) |
| CRC mortality | 44 | 25 | 43 | 0.57 (0.45–0.72) |
| Secondary endpoints | | | | |
| All-cause mortality | 1124 | 1093 | 3 | 0.051 |
| Incidence of distal CRC | 98 | 48 | 50 | 0.5 (0.42–0.59) |
| Incidence of proximal CRC | 51 | 50 | 2 | 0.97 (0.80–1.17) |

Discussion

Over a F/U period of 11y, the incidence of CRC was reduced by a third, and CRC-related mortality was reduced by over 40% in patients undergoing once-only FS screening. For cancers localized to the sigmoid and rectum, the incidence was reduced by half. Furthermore, economic analysis indicated that a single FS offered to patients aged between 55 and 64y was cost-effective, as it negated treatment costs by reducing the incidence. These findings suggest that specific patient populations may derive enduring substantial benefit from once-only FS. Results should be evaluated in the context of the current national screening programme, based on faecal occult blood testing (FOBT). If sufficiently applicable and cost-effective, once-only FS is likely to offer superior outcomes, when compared to FOBT, particularly as it allows the opportunity for both surveillance and treatment. (See Table 8.1.)

Problems

- The trial did not employ population-based screening but specifically recruited patients who responded to a questionnaire indicating that they would accept screening. Thus, compliance rates in the study are likely to have been overestimated;
- The incidence of proximal colonic cancers was not reduced through this screening method.

Gastric cancer: *Helicobacter pylori* eradication

Helicobacter pylori eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial.

AUTHORS: Wong B, Lam S, Wong W et al.

REFERENCE: JAMA (2004) 291, 187–94.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In *H. pylori* carriers without precancerous lesions on presentation, eradication therapy decreases the development of gastric cancer.

Impact

Despite persuasive evidence implicating *H. pylori* as the main cause of gastric cancer, clinical benefits of eradication therapy in asymptomatic *H. pylori* carriers without peptic ulcer is not well established. This was the first population-based study to demonstrate that eradication therapy reduced the risk of gastric cancer in subjects without precancerous lesions already. However, the role of *H. pylori* eradication in preventing gastric cancer continues to be debated.

Aims

H. pylori infection is an established risk factor for the development of gastric cancer. This study aimed to determine whether treating *H. pylori* infection reduces the incidence of gastric cancer.

Methods

Subjects: 1,630 healthy carriers of *H. pylori* infection, from centres in Fujian Province, China. A total of 988 patients were without precancerous lesions (gastric atrophy, intestinal metaplasia, or gastric dysplasia).

Inclusion criteria: Healthy subjects with normal endoscopy and confirmed *H. pylori* infection:

- Endoscopic gastric antral biopsy positive for rapid urease test;
- *H. pylori* confirmed on histology of gastric antral biopsy.

Exclusion criteria:

- History of *H. pylori* eradication therapy;
- Ulcer on endoscopy;
- Equivocal or negative rapid urease test or histology;
- Age <35y and >65y;
- Severe co-morbidity.

Groups:

- Treatment: received triple therapy, followed by carbon-13 urea breath test (^{13}C -UBT). Those with unsuccessful eradication received quadruple therapy, followed by repeat ^{13}C -UBT in 6wk ($n = 817$);
- Placebo ($n = 813$).

Primary endpoint: Incidence of gastric cancer during F/U.

Secondary endpoints: Incidence of gastric cancer in subjects with or without precancerous lesions.

Follow-up: 6-monthly review, biannual ^{13}C -UBT for *H. pylori* status. Repeat endoscopy at 5y or when upper GI symptoms appeared. Total F/U = 7.5y.

Results

Table 8.2 Summary of results

| Primary endpoint | Placebo ($n = 813$) | <i>H. pylori</i> eradication ($n = 817$) | <i>p</i> |
|-----------------------------|-----------------------|--|----------|
| New cases of gastric cancer | 11 | 7 | 0.33 |
| Secondary endpoint | Placebo ($n = 503$) | <i>H. pylori</i> eradication ($n = 485$) | |
| New cases of gastric cancer | 6 | 0 | 0.02 |

Discussion

After 7.5y of F/U, gastric cancer developed in seven subjects who received *H. pylori* eradication and in 11 in the placebo group. Among 18 new cases of gastric cancer, six developed in subjects without precancerous lesions, whereas 12 developed in those with such lesions. None in the *H. pylori*-treated group without premalignant lesions developed gastric cancer during the study period, suggesting that eradication therapy was beneficial in this group. However, *H. pylori* treatment had no benefit in subjects with precancerous lesions. It could be argued that, during the development of precancerous lesions, the benefit of *H. pylori* eradication diminishes, and a 'point of no return' may be reached. Other studies have demonstrated that *H. pylori* eradication results in regression of gastric atrophy and intestinal metaplasia in 15–30% of cases. Therefore, a larger sample size and longer F/U are required to investigate whether *H. pylori* eradication is beneficial in this subgroup. (See Table 8.2.)

Problems

- A small number of cancers were detected, and the duration of F/U was too short for this study to be conclusive. Longer F/U would have been particularly useful in investigating the effect of eradication therapy in those with precancerous lesions at the time of initial endoscopy;
- The study was based in a high-risk population. It is unclear whether these results are applicable to low-risk areas in Western countries.

Peptic ulcer disease: *Helicobacter pylori* eradication

Eradication therapy for peptic ulcer disease in *Helicobacter pylori*-positive patients.

AUTHORS: Ford A, Delaney B, Forman D et al.

REFERENCE: *Cochrane Database Syst Rev* (2006) 2, CD003840.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 1a.

Key message

All *H. pylori*-positive peptic ulcer disease patients should receive eradication therapy.

Impact

The seminal discovery that *H. pylori* infection is the cause of 95% of duodenal, and 70% of gastric, ulcers radically changed the management of dyspepsia. The majority of peptic ulcers can now be cured by *H. pylori* eradication therapy, and surgical interventions are rarely indicated.

Aims

RCTs of short- and long-term treatment of peptic ulcer disease in *H. pylori*-positive adults were analysed to assess the proportion of patients with peptic ulcers, and the proportion of patients who remained free from relapse after eradication therapy.

Methods

Trials included: 56 of 63 eligible trials.

Inclusion criteria: RCTs of short- and long-term treatment of peptic ulcer disease in *H. pylori*-positive adults:

- ≥ 1 wk of *H. pylori* eradication;
- Comparison with ulcer healing drug, placebo, or no treatment;
- Patients assessed at 2wk or after eradication therapy.

Exclusion criteria: Trials from which data extraction was not possible.

Types of interventions:

- Proton pump inhibitor (PPI) dual or triple therapy (one or two antibiotics);
- H₂ receptor antagonist triple therapy;
- Bismuth triple or quadruple therapy;
- PPI, H₂ receptor antagonists, bismuth salts, sucralfate, antacids, as monotherapy;
- Placebo;
- No treatment.

Primary endpoints:

- Proportion of ulcers healed initially;
- Proportion of patients free from recurrence, following successful healing.

Results

Table 8.3 Summary of results

| Primary endpoints | Eradication therapy vs ulcer healing drugs | Eradication therapy vs no treatment |
|--|--|-------------------------------------|
| Duodenal ulcer persisting with therapy | RR: 0.66 95% CI: 0.58–0.76 | RR: 0.37 95% CI: 0.26–0.53 |
| Duodenal ulcer recurring with therapy | RR: 0.73 95% CI: 0.42–1.25 | RR: 0.20 95% CI: 0.15–0.26 |
| Gastric ulcer persisting with therapy | RR: 1.25 95% CI: 0.88–1.76 | – |
| Gastric ulcer recurring with therapy | – | RR: 0.29 95% CI: 0.20–0.42 |

Discussion

About 10% of the Western population develops a gastric or duodenal ulcer during their lifetime. The cost to health care runs into billions of pounds. In the 1970s and 80s, therapy for peptic ulcer disease was mainly aimed at reducing acid secretion using H₂ receptor antagonists and PPIs. Recognition of the role of *H. pylori* in the development and recurrence of peptic ulcers and confirmation that this could be prevented by eradication of the organism have transformed the management of peptic ulcer disease. This review concluded that eradication therapy was clearly indicated in *H. pylori*-positive peptic ulcer disease, as there were definite benefits in terms of ulcer healing and prevention of recurrence. Benefits were more marked in duodenal ulcers. This was consistent with international guidelines. Use of *H. pylori* eradication therapy reduced the use of health-care resources during F/U, compared with conventional ulcer healing drugs and therefore should be the preferred approach from a health economic perspective. (See Table 8.3.)

Problems

- This review reported ulcer healing rates of 75–85%, and ulcer recurrence rates of 12–14%. These figures are much lower than previous systematic reviews, which report healing rates of 90–95% and recurrence rates of <10%. This was due to the analysis used where all patients lost to F/U in the trials were assumed to be treatment failures;
- The review found no significant benefit in symptom relief with *H. pylori* eradication therapy over other regimens. The number of trials included reporting this outcome was small, and none of the trials evaluated symptoms beyond 6wk, thereby potentially overlooking the long-term effects of *H. pylori* eradication.

Peptic ulcer disease: managing antiplatelet bleeding risk

Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding.

AUTHORS: Chan F, Ching J, Hung L et al.

REFERENCE: *N Engl J Med* (2005) 352, 238–44.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients taking aspirin with bleeding peptic ulcers, once the ulcer has healed, restarting aspirin, in combination with a proton pump inhibitor, is better than introducing clopidogrel in preventing recurrent bleeding.

Impact

In the past two decades, many millions have started taking aspirin to prevent myocardial infarction and stroke. Aspirin, even at low doses, doubles the risk of upper GI bleeding. Two strategies that allow maintenance of cardiovascular protection and minimize GI adverse events were compared in this study. Based on the firm evidence provided, combination of aspirin with a proton pump inhibitor should be the standard management in this situation. The results raise doubt about the GI safety of clopidogrel.

Aims

PPI therapy heals ulcers and reduces the risk of bleeding. Clopidogrel, an effective antiplatelet agent, does not induce ulcers. Therefore, patients who have had one episode of GI bleeding from ulcers, while on aspirin, can either receive the combination of aspirin and a PPI, or clopidogrel (instead of aspirin). This study aimed to compare the effectiveness of these two strategies in the prevention of recurrent bleeding in high-risk patients.

Methods

Patients: 320 patients at one centre in Hong Kong.

Inclusion criteria: Consecutive users of low-dose aspirin (≤ 325 mg/d) with upper GI bleeding due to peptic ulcer (confirmed on index endoscopy):

- Triple therapy if *H. pylori*-positive;
- Withdrawal of aspirin and PPI therapy to heal the ulcer;
- Healed ulcer plus successful *H. pylori* eradication on repeat endoscopy at 8wk.

Exclusion criteria: Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, and anticoagulants.

Groups:

- Clopidogrel (75mg) plus placebo bd (n = 161);
- Aspirin (80mg) plus esomeprazole (20mg) bd (n = 159).

Primary endpoint: Recurrent ulcer bleeding with endoscopically documented ulcers or erosions.

Secondary endpoints: Lower GI bleeding.

Follow-up: 12mo.

Results

Table 8.4 Summary of results

| Primary endpoint | Clopidogrel + placebo | Aspirin + esomeprazole | p |
|--|-------------------------|------------------------|-------|
| Cumulative incidence of recurrent ulcer bleeding | 8.6% (95% CI 4.1–13.1%) | 0.7% (95% CI 0–2.0%) | 0.001 |
| Secondary endpoint | | | |
| Cumulative incidence of lower GI bleeding | 4.6% (95% CI 1.3–7.9%) | 4.6% (95% CI 1.3–8.0%) | 0.98 |

Discussion

A previous study reported about 15% of patients with a history of ulcer bleeding to develop recurrent bleeding within 1y of aspirin therapy. Current opinions regarding GI safety of clopidogrel have been based on 2° analysis of studies that did not use prespecified criteria to report GI complications. This study's findings challenge the American College of Cardiology/American Heart Association guidelines, which recommend the use of clopidogrel in patients with major GI side effects from aspirin. The majority (71%) of rebleeding episodes were from recurrent ulcers at the same location as seen during the initial endoscopy. The mechanisms leading to recurrent bleeding among patients receiving clopidogrel are unknown. Clopidogrel inhibits platelet-derived growth factors, which may impair ulcer healing and induce recurrent bleeding from the previously damaged mucosa. Alternatively, co-morbidity may predispose patients to the development of ulcers in the absence of *H. pylori* or NSAIDs. (See Table 8.4.)

Problems

- The study did not include a group of patients who were restarted on aspirin without PPI, as this was considered unethical. Therefore, it was not possible to assess whether clopidogrel was safer than aspirin;
- The efficacy of PPI is known to vary among ethnic groups, and this may have influenced the significance of the results;
- Study drugs were repackaged from the commercially available form; this may have influenced their therapeutic effects.

Peptic ulcer disease: endoscopic control of bleeding

Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials.

AUTHORS: Marmo R, Rotondano G, Piscopo R *et al.*

REFERENCE: *Am J Gastroenterol* (2007) 102, 279–89.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Treatment using a thermal probe/haemoclip as monotherapy is as effective as dual-modality therapy. Therefore, routine combined endoscopic therapy is not recommended. In patients with active arterial bleeding, dual therapy assures a higher rate of initial haemostasis.

Impact

Combined therapy using adrenaline injection plus thermal coagulation is increasingly being offered as the gold standard management for bleeding peptic ulcers. However, adrenaline injection is still the most widely used treatment. While this meta-analysis supports dual therapy, it also suggests that, if a single modality of endoscopic intervention is to be delivered, it should be thermal coagulation. Therefore, every endoscopist should become proficient with thermal coagulation treatment.

Aims

Endoscopic techniques of haemostasis, such as injection, thermal, and mechanical methods, are complementary in the management of bleeding peptic ulcers. This study aimed to assess the efficacy of dual vs single endoscopic intervention in improving clinical outcomes.

Methods

Studies: 20 studies.

Inclusion criteria: Studies comparing efficacy of dual endoscopic therapy vs any other form of endoscopic monotherapy:

- Patients with bleeding from peptic ulcer;
- Stigmata of bleeding at the ulcer base (active bleeding, visible vessel, or adherent clot).

Exclusion criteria: Studies without detail on safety of techniques used.

Groups: Injection of two agents vs injection of single agents. Four groups:

- Dual therapy vs controls; dual therapy vs injection therapy; dual therapy vs thermal coagulation; dual therapy vs mechanical treatment.

Primary endpoint:

- Control of bleeding;
- Risk of rebleeding;
- Risk of emergency surgery;
- Risk of death.

Secondary endpoints: Procedure-related complications.

Results

Table 8.5 Summary of results

| Primary endpoints | Dual vs controls OR (95% CI) | Dual vs injection OR (95% CI) | Dual vs thermal OR (95% CI) | Dual vs mechanical OR (95% CI) |
|----------------------------|---------------------------------|----------------------------------|--------------------------------|-----------------------------------|
| Rebleeding | 0.59 (0.44–0.80) | 0.36 (0.18–0.73) | 0.67 (0.40–1.20) | 1.04 (0.45–2.45) |
| Emergency surgery | 0.66 (0.49–0.89) | 0.40 (0.19–0.83) | 0.89 (0.45–1.76) | 0.49 (0.50–4.87) |
| Death risk | 0.68 (0.46–1.02) | 0.88 (0.35–2.22) | 0.51 (0.24–1.10) | 1.28 (0.34–4.86) |
| Secondary endpoints | Dual therapy | Monotherapy | <i>p</i> | |
| Procedure-induced bleeding | 18/1,069 | 18/1,068 | >0.05 | |
| Perforation | 7/1,069 | 0/1,068 | 0.03 | |

Discussion

Evolution of endoscopic techniques has allowed 1° haemostasis to be achieved in up to 95% of bleeding peptic ulcers. Adrenaline injection is simple, cheap, and safe. However, thermal coagulation and haemoclip were more effective. As different interventions may be complementary, combination of adrenaline injection and thermal coagulation is increasingly offered as the gold standard. In high-risk peptic ulcer bleeding, this study confirmed that dual endoscopic therapy (additional thermal probe or haemoclip application) was superior to adrenaline injection alone. However, when bleeding had first been controlled using thermal or mechanical treatment, further injection therapy had no additional benefit. Therefore, the logical approach should be to use thermal probes first; if this achieves haemostasis, no further treatment is necessary. In ongoing bleeds during endoscopy, initial adrenaline injection, followed by thermal coagulation, achieves better control of bleeding. Routine application of combined endoscopic therapy in all patients is not warranted. (See Table 8.5.)

Problems

- The number of studies and patients was not large enough to have sufficient power to detect small (but potentially significant) differences between dual therapy and thermal coagulation;
- Dual therapy is associated with an increased risk of perforation;
- Expertise and sound judgement are of paramount importance when treating high-risk bleeding peptic ulcer patients. Haemoclips are effective but also require technical expertise, limiting their applicability.

Upper gastrointestinal bleeding: red cell transfusion

Transfusion strategies for acute upper gastrointestinal bleeding.

AUTHORS: Villanueva C, Colomo A, Bosch A *et al.*

REFERENCE: *N Engl J Med* (2013) **368**, 11–21.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A restrictive threshold (Hb <7g/dL) for red cell transfusion significantly improves patient survival and reduces the risk of further bleeding events, when compared to liberal transfusion strategies (Hb <9g/dL), in acute upper GI haemorrhage.

Impact

Acute upper GI bleeding is a common indication for red cell transfusion. This was the first RCT to demonstrate that adopting a lower Hb threshold prior to initiation of red cell transfusion conferred superior overall patient outcome in the context of acute upper GI bleeding. This trial has led to an appraisal of the use of blood products in resuscitation; subsequent systematic reviews have considered the benefits, as well as disadvantages, of red cell transfusion.

Aims

Observational studies have proposed that liberal transfusion policies are associated with adverse patient outcomes, due to fluid overload, coagulopathy, or increased portal pressures in chronic liver disease. This trial aimed to investigate the impact on mortality, rebleeding risk, and complication rates of a restrictive vs liberal transfusion threshold in acute upper GI bleeding.

Methods

Patients: 889 patients at a single centre in Barcelona.

Inclusion criteria:

- Patients with haematemesis, melaena, or both;
- Age >18y;
- Rockall score >0;
- Hb <12g/dL.

Exclusion criteria:

- Exsanguinating haemorrhage;
- ACS, vasculopathy, stroke, or TIA;
- Transfusion within previous 90d;
- Recent trauma or surgery;
- Pregnancy.

Groups:

- Restrictive strategy group ($n = 444$): threshold for transfusion Hb 7g/dL. Target post-transfusion range Hb 7–9g/dL;
- Liberal strategy group ($n = 445$): threshold for transfusion Hb 9g/dL. Target post-transfusion range Hb 9–11g/dL.

Primary endpoint: Mortality from any cause within 45d.

Secondary endpoints:

- Rebleeding rate;
- Rate of in-hospital complications.

Results

Table 8.6 Summary of results

| Primary endpoint | Liberal strategy (%) | Restrictive strategy (%) | <i>p</i> |
|---------------------|----------------------|--------------------------|----------|
| Mortality | 9 | 5 | 0.02 |
| Secondary endpoints | | | |
| Rebleeding rate | 16 | 10 | 0.01 |
| Complications | 48 | 40 | 0.02 |

Discussion

Previous observational and small controlled studies had suggested that restrictive transfusion strategies may improve outcome in critically ill patients or in those with hypovolaemic anaemia. Results from this RCT provide convincing evidence that a conservative approach to provision of red cells may confer superior outcome in acute upper GI haemorrhage, with respect to patient survival, rebleeding risk, and rate of in-hospital complications. The observed differences in mortality and rebleeding rates between the two groups may be related to transfusion-associated complications in the liberal strategy group, including circulatory overload, transfusion reactions, and increased portal pressures in cirrhotic patients. (See Table 8.6.)

Problems

- Patients with exsanguinating upper GI haemorrhage and those with low rebleeding risk were not included in the study. The benefit of restrictive strategies in these populations therefore remains unclear and warrants further research;
- Hb was the only measured endpoint to guide transfusion decisions. In clinical practice, a more holistic approach is required when determining the need for transfusion, including consideration of a patient's co-morbidities (CAD) and the speed and volume of acute blood loss (postural hypotension).

Upper gastrointestinal bleeding: intravenous proton pump inhibitor

APPE STUDY: Administration of intravenous *Proton Pump* inhibitor prior to *Endoscopy* in patients with upper gastrointestinal bleeding.

AUTHORS: Lau J, Leung W, Wu J *et al.*

REFERENCE: *N Engl J Med* (2007) 356, 1631–40.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Infusion of a PPI before endoscopy leads to early resolution of upper GI bleeding, also reducing the need for endoscopic therapy and the duration of hospital stay.

Impact

Endoscopic therapy is the key step in the management of suspected upper GI bleeding and has an established role in the care of these patients. However, out-of-hours endoscopy is not uniformly available in hospitals in the UK. Early presumptive infusion of a PPI may become a common practice in patients with suspected upper GI bleeding.

Aims

A neutral gastric pH is critical for the stability of clot over bleeding arteries. Therefore, it has been proposed that earlier acid suppression with PPI therapy for any GI bleeds (before the cause is known) may lead to better outcomes. This study aimed to investigate the effect of presumptive infusion of omeprazole (before endoscopy) on the need for endoscopic therapy.

Methods

Patients: 638 patients at one centre in Hong Kong.

Inclusion criteria: Consecutive patients with overt signs of upper GI bleeding:

- Age >16y;
- Fresh haematemesis and/or melaena;
- Haemodynamically stable (after volume resuscitation, if and as required).

Exclusion criteria: Chronic low-dose aspirin use.

Groups: Both groups received 80mg IV bolus, followed by 8mg/h infusion for 72h:

- Omeprazole ($n = 319$);
- Placebo ($n = 319$).

Primary endpoint: Control of bleeding at the time of endoscopy.

Secondary endpoints:

- Transfusion requirement;
- Rate of rebleeding;
- Need for emergency surgery;
- 30d mortality;
- Duration of hospital stay.

Follow-up: 30d from the time of admission or until the time of discharge (if >30d), or death.

Results**Table 8.7** Summary of results

| Primary endpoints | Placebo | Omeprazole | p |
|---------------------------------|---------|------------|-------|
| Need of endoscopic therapy | 28.4% | 19.1% | 0.007 |
| Active bleeding on endoscopy | 14.7% | 6.4% | 0.01 |
| Clean base ulcer on endoscopy | 47.4% | 64.2% | 0.001 |
| Secondary endpoints | | | |
| Mean units of blood transfusion | 1.88 | 1.54 | 0.1 |
| Rebleeding | 2.5% | 3.5% | 0.5 |
| Need of emergency surgery | 1.26% | 0.95% | 1.0 |
| 30d mortality | 2.52% | 2.22% | 0.8 |
| <3d hospital stay | 60.5% | 49.2% | 0.005 |

Discussion

A systematic review had suggested that PPI therapy reduced the risk of rebleeding and surgery in patients with bleeding peptic ulcer. It is now standard practice to perform an early endoscopy in patients with upper GI bleeding, with an intention to establish the underlying aetiology and to treat (endoscopic haemostatic methods), as well as to assess the risk of rebleeding (active bleeding, visible vessel at endoscopy) and mortality (using Rockall score). Patients confirmed to have peptic ulcer and estimated to be at high risk of rebleeding were treated with IV PPI for 72h. This study suggested that it was beneficial to treat all cases of upper GI bleeding with IV PPI, even pre-endoscopy. Early PPI treatment may assist endoscopic diagnosis and may reduce the need for endoscopic therapy. (See Table 8.7.)

Problems

- There were no significant differences in clinically important secondary endpoints such as rebleeding, need for surgery, and death;
- The proportion of patients with bleeding due to peptic ulcer was much higher than that seen in many Western countries. So the impact of PPI therapy will vary, depending on the case mix of patients with differing aetiologies of upper GI bleeding;
- Previous studies had suggested that PPIs perform better for peptic ulcer bleeds in Asian patients, compared with other ethnic groups. Therefore, the findings cannot be extrapolated to all patient groups;
- The cost-effectiveness of early IV PPI was not assessed.

Variceal bleeding: primary prevention

Comparison of endoscopic ligation and propranolol for the primary prevention of variceal bleeding.

AUTHORS: Sarin S, Lamba G, Kumar M *et al.*

REFERENCE: *N Engl J Med* (1999) **340**, 988–93.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with high-risk oesophageal varices, endoscopic ligation of the varices is safe and effective for the 1° prevention of variceal bleeding.

Impact

This study highlighted the superiority of variceal banding. As β -blockers are inexpensive, and generalists are able to prescribe them, some guidelines still recommend non-selective β -blockers as the first-line treatment for 1° prevention of variceal bleeding. In subjects who are intolerant to, or non-compliant with, β -blocker therapy, prophylactic variceal banding is now an established intervention.

Aims

β -blockers and endoscopic variceal ligation have independently been shown to decrease the risk of first-episode variceal bleeding. This study compared propranolol therapy with banding for the 1° prevention of variceal bleeding.

Methods

Patients: 89 patients at one centre in India.

Inclusion criteria: Patients with large varices who were at high risk of bleeding:

- Varices >5mm in diameter;
- At least one 'red sign' (cherry-red spot, red wale, haematocystic spot);
- No history of haematemesis or melaena.

Exclusion criteria:

- Concomitant hepatoma;
- On antiviral therapy;
- Contraindications to β -blockers.

Groups:

- Propranolol group: 40mg/d, to increase daily until resting HR decreases by 25% of the baseline (or SBP <80mmHg, HR <55) ($n = 44$);
- Band ligation group: 3–9 bands placed in the lower 5–7cm of variceal columns. Procedure was repeated weekly to obliterate varices ($n = 45$).

Primary endpoint: Variceal bleeding.

Secondary endpoints:

- Transfusion requirement;
- Death.

Follow-up: 18mo.

Results

Table 8.8 Summary of results

| Primary endpoint | Propranolol (<i>n</i> = 44) | Banding (<i>n</i> = 45) | <i>p</i> |
|---|---------------------------------|-----------------------------|----------|
| Cumulative probability of variceal bleeding in 18mo | 43% | 15% | 0.04 |
| Secondary endpoints | | | |
| Number of patients needing blood transfusion | 1 | 7 | 0.03 |
| Mean number of transfusions per patient | 0.1 | 0.4 | 0.03 |
| Proportion of patients hospitalized | 27% | 11% | 0.09 |
| Deaths | 11% | 11% | 0.8 |

Discussion

Although β -blockers have proven efficacy in preventing bleeding from varices, they have a variable and unpredictable effect on hepatic venous pressure gradient (HVPG), and hence the portal pressure. β -blocker therapy needs to be given for prolonged periods, and long-term non-compliance raises the risk of bleeding to pretreatment levels. In addition, contraindications and intolerance limit the use of propranolol. This study showed endoscopic variceal ligation to be more effective and safer than sclerotherapy. Varices could be obliterated within about a month. Therefore, ligation offered a distinct advantage over lifelong β -blocker therapy. In this study, the risk of bleeding was lower with ligation than with propranolol. No serious complication occurred due to banding, but two patients in the propranolol group stopped treatment due to side effects. (See Table 8.8.)

Problems

- The efficacy of β -blockers in patients without cirrhosis is less established. When patients without cirrhosis were excluded (leaving 41 patients in each group), the actuarial probability of bleeding was 43% in the propranolol group and 17% in the banding group (not significant; $p = 0.08$);
- There may be ethnic variations in the metabolism of propranolol which, in turn, may influence its efficacy. Therefore, the findings of this study may not be entirely applicable to a Caucasian population;
- The costs of each strategy were not compared.

Gastrointestinal bleeding with cirrhosis: antibiotic prophylaxis

Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis.

AUTHORS: Bernard B, Grange J, Khac E *et al.*

REFERENCE: *Hepatology* (1999) **29**, 1655–61.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

In patients with cirrhosis and upper gastrointestinal (GI) bleeding, antibiotic prophylaxis for 7d significantly increases short-term survival.

Impact

This meta-analysis showed, for the first time, that systemic antibiotic prophylaxis improved survival in patients with cirrhosis and GI haemorrhage. Benefits gained by this simple and inexpensive measure are comparable to endoscopic interventions in their importance. Current guidelines recommend antibiotic prophylaxis in these patients.

Aims

Bacterial infections complicate 35–66% of GI bleeding episodes in patients with cirrhosis, and these predict rebleeding and poor outcome. The aim of this meta-analysis was to assess the efficacy of antibiotic prophylaxis in the prevention of infections and its effect on survival rates in patients with cirrhosis and upper GI bleeding.

Methods

Trials: Five trials (534 patients).

Inclusion criteria: Prospective randomised trials:

- Patients with cirrhosis and GI bleeding.

Exclusion criteria:

- Trials comparing two different treatments;
- Trials including patients without GI bleeding.

Groups:

- Antibiotic group: treatment for 4–10d (n=264);
- No antibiotic group (n=270).

Follow-up: Mean of 12d.

Primary endpoints:

- Proportion of patients free of infection;
- Proportion of patients free of spontaneous bacterial peritonitis;
- Proportion of patients surviving.

Results

Table 8.9 Summary of results

| Primary endpoints | No antibiotic prophylaxis | Antibiotic prophylaxis | p |
|--|---------------------------|------------------------|--------|
| Proportion free of infection | 55% | 86% | <0.001 |
| Proportion free of spontaneous bacterial peritonitis | 87% | 95% | 0.006 |
| Proportion of patients surviving | 76% | 85% | 0.004 |

Discussion

Although the incidence of infections, including spontaneous bacterial peritonitis, varied between trials, the efficacy of antibiotic prophylaxis was clearly established. Benefits were more marked in patients with more severe liver disease. Sensitivity analysis suggested that absorbable antibiotics were superior. Antibiotic prophylaxis also increased the mean survival rate by 9% (95% CI 2.9–15.3%). Considering the fact that overall mortality in cirrhosis with upper GI bleeding can be up to 30%, the benefits of antibiotic prophylaxis were highly significant. The risk of short duration of treatment (4–10d) seems to be very low. Development of resistant strains in those receiving antibiotics was not observed. Moreover, one study demonstrated that the cost of antibiotic prophylaxis was lower than the cost of treatment of infection. (See Table 8.9.)

Problems

- There was significant heterogeneity between the control groups for the proportion of individuals free of infection or spontaneous bacterial peritonitis. This was due to variations in the severity of underlying liver disease included in the different trials;
- Data on adverse events of treatment were not consistently recorded in the trials.

Alcoholic hepatitis: corticosteroids

Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis (AH): individual data analysis of the last three randomized placebo-controlled double blind trials of corticosteroids in severe AH.

AUTHORS: Mathurin P, Mendenhall L, Carithers RJ et al.

REFERENCE: *J Hepatol* (2002) **36**, 480–7.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

In patients with severe alcoholic hepatitis, corticosteroid therapy improves short-term survival. For every five patients treated, corticosteroids prevents one death.

Impact

This study argues that, if patients are chosen for corticosteroid therapy using Maddrey discriminant factor, then therapy proves to be effective. It is still unclear whether histological or clinical criteria should be used to diagnose alcoholic hepatitis. Use of Maddrey discriminant factor in clinical practice, as well as corticosteroid therapy, in this condition is increasing. However, debate regarding the role of corticosteroid continues to polarize opinions and clinicians.

Aims

RCTs that evaluated corticosteroids in alcoholic hepatitis (AH) had used a variety of definitions, inclusions, and exclusions. This study analysed individual data of patients with severe AH with Maddrey discriminant factor (DF) ≥ 32 from the last three trials to investigate the effect of corticosteroid treatment on short-term survival.

Methods

Trials: Three RCTs (215 patients).

Inclusion criteria:

- Severe AH with Maddrey DF ≥ 32 (DF = bilirubin in mg/dL + prothrombin time above control in seconds $\times 4.6$);
- Diagnosis of AH based on clinical criteria or liver biopsy.

Exclusion criteria:

- Active peptic ulcer;
- Active infection.

Groups: Corticosteroid regime in three studies included prednisolone 60mg/d to taper 4wk or 40mg/d for 28d, and methylprednisolone 32mg/d for 28d:

- Corticosteroid group ($n = 113$);
- Placebo group ($n = 102$).

Primary endpoint: Survival at 28d.

Follow-up: 28d from the onset of treatment or death.

Results

Table 8.10 Summary of results

| Primary endpoint | Placebo | Corticosteroid | p |
|--|---------|----------------|-------|
| Proportion who survived at 28d | 65.1% | 84.6% | 0.001 |
| Secondary endpoint | | | |
| Median difference in Maddrey DF between d28 and d0 | -16 | -25 | 0.002 |

Discussion

Two meta-analyses evaluating the role of steroid therapy in AH had included trials that were too heterogeneous and drew contradictory conclusions. This study highlighted factors regarding the case definition, assessment of severity, and exclusions that may explain these inconsistencies. Maddrey DF is a well-validated measure of severity, while hepatic encephalopathy correlates poorly with clinical outcome. Studies that included patients with encephalopathy failed to demonstrate benefits of steroid therapy. Similarly, the protective effect of steroids depends upon the exclusion of patients with GI bleeding. Using data from patients with Maddrey DF ≥ 32 , the authors demonstrated that corticosteroid-treated patients had a higher survival in each individual trial included in the analysis. Benefit of treatment was highly significant overall. Multivariate analysis identified corticosteroid treatment ($p < 0.01$) as an independent predictor of favourable outcome in these patients. (See Table 8.10.)

Problems

- Data from only three trials were suitable for analysis, in contrast with 11 and 13 trials included in two previous meta-analyses;
- The definition of AH was based on histology in one trial, while liver biopsy was not required in the other two. This adds significant heterogeneity to the study population;
- Protective effects of corticosteroids depend on the exclusion of patients with GI bleeding. One of the trials did not exclude these patients.

Alcoholic hepatitis: combination therapy

Glucocorticoids plus *N*-acetylcysteine in severe alcoholic hepatitis.

AUTHORS: Nguyen-Khac E, Thevenot T, Piquet M et al.

REFERENCE: *N Engl J Med* (2011) 365, 1781–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Dual therapy with *N*-acetylcysteine, in addition to glucocorticoids, decreased 1mo mortality in patients with severe alcoholic hepatitis, with fewer infections in this versus the steroid alone group.

Impact

Mortality from alcoholic liver disease has increased in the UK over the past decades. Alcoholic hepatitis is a severe inflammatory disorder, which carries a high mortality rate (35% at 6mo). This randomized controlled trial used a combination of two commonly used therapeutic agents glucocorticoid and *N*-acetylcysteine to achieve an improved short-term survival.

Aims

Central to the pathogenesis of AH is hepatocyte injury through oxidative stress, related to free radical production and alcohol-induced upregulation of pro-inflammatory cytokines. Mitochondrial depletion of glutathione, a naturally occurring antioxidant, further exacerbates this process. *N*-acetylcysteine (NAC) is known to replenish glutathione levels and acts as a free radical scavenger. This study aimed to establish whether addition of NAC to steroid therapy improved 6mo mortality in patients with severe AH.

Methods

Patients: 174 patients at 11 University Hospitals in France.

Inclusion criteria:

- Age >18y;
- Alcohol intake >50g/d in the preceding 3mo;
- Maddrey DF ≥ 32 ;
- Liver histology in keeping with a diagnosis of AH.

Exclusion criteria:

- Hepatorenal syndrome/hepatocellular carcinoma;
- Causes of chronic liver disease other than alcohol (drug-induced, hereditary, autoimmune, or infective causes);
- Active cancer;
- Allergy to NAC;
- GI bleed within the preceding 4d;
- Overwhelming bacterial infection.

Groups:

- Prednisolone only ($n = 91$);
- Prednisolone plus NAC ($n = 89$).

Primary endpoint: Survival at 6mo.

Secondary endpoints:

- Survival at 1mo and 3mo;
- Changes in bilirubin levels at 7d and 14d of treatment.

Table 8.11 Summary of results

| Primary endpoint | Steroids only | Steroids plus NAC | <i>p</i> |
|---------------------|---------------|-------------------|----------|
| 6mo mortality | 38% | 27% | 0.07 |
| Secondary endpoints | | | |
| 1mo mortality | 24% | 8% | 0.006 |
| 3mo mortality | 34% | 22% | 0.06 |

Discussion

This RCT addressed the paradigm of oxidative stress as a major causative factor in the pathogenesis of AH. NAC may confer a protective effect on hepatocytes through its antioxidant properties. In this study, combination therapy with NAC and prednisolone resulted in a significant reduction in 1-mo mortality, lending support to the hypothesis that NAC is hepatoprotective through increasing glutathione levels and reducing free radical formation. However, no reduction in 3- or 6-mo mortality means that further trials involving longer durations of NAC therapy may reveal a significant long-term improvement in patient outcome. A reduction in serum bilirubin levels at 7d and 14d after treatment is a marker of favourable prognosis, with those responding to therapy having an increased survival rates at 6mo. One of the concerns regarding glucocorticoid therapy is predisposition to infection; however, infections were less frequent in the prednisolone plus NAC vs the prednisolone only group. (See Table 8.11.)

Problems

- This study failed to confirm a statistically significant long-term survival benefit with the addition of NAC to steroid therapy. Therefore, the clinical impact of improved 1-mo survival is unclear;
- The study lacked statistical power to demonstrate a difference in survival at 3mo and 6 mo. If patients survive at 6mo, then they may be suitable for definitive treatment such as transplantation.

Ascites: fluid replacement following paracentesis

Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis.

AUTHORS: Gines A, Fernandez-Esparrach G, Monescillo A et al.

REFERENCE: *Gastroenterology* (1996) 111, 1002–10.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients undergoing large-volume therapeutic paracentesis, 20% albumin solution is the best plasma expander to prevent post-paracentesis circulatory dysfunction and associated complications.

Impact

This was one of the first studies to highlight the role of 20% albumin in the management of ascites and related complications. Albumin is now accepted as the best plasma expander in cirrhosis, although there is incomplete agreement regarding the threshold for its use and the magnitude of its impact.

Aims

Large-volume paracentesis with plasma volume expansion is an effective and safe therapy for tense ascites in cirrhosis. This study aimed to compare the efficacy of albumin, dextran 70, and polygeline in preventing post-paracentesis circulatory dysfunction and its consequences.

Methods

Patients: 289 patients at 12 hospitals in Spain, Italy, and Argentina.

Inclusion criteria: Patients with cirrhosis and tense ascites.

Exclusion criteria:

- Bilirubin >170 micromol/L, prothrombin time <40%, platelets <40,000/mm³, serum creatinine >280 micromol/L;
- GI bleeding within the preceding month;
- Hepatocellular carcinoma;
- Respiratory, cardiac, or renal disease.

Groups: All groups had 8g/L of ascitic fluid drained; 50% of the dose was given within the first 2h, and the rest 6–8h after paracentesis;

- Albumin: 20% albumin solution ($n = 97$);
- Dextran 70: 6g of dextran 70 per 100mL of dextrose solution ($n = 93$);
- Polygeline: 3.5% saline solution of polygeline ($n = 99$).

Primary endpoint: Post-paracentesis circulatory dysfunction:

- Increase in plasma renin activity (PRA) of >50% of the pretreatment value to a level of >4ng/mL/h.

Secondary endpoints: Clinical outcome in those with and without post-paracentesis circulatory dysfunction:

- Time to first readmission;
- Survival.

Follow-up: Up to 6mo.

Results

Table 8.12 Primary endpoint

| Primary endpoint | Albumin group | Dextran 70 group | Polygeline group | <i>p</i> |
|---|---------------|------------------|------------------|----------|
| Proportion developing post-paracentesis circulatory dysfunction | 18.5% | 34.4% | 37.8% | <0.02 |

Table 8.13 Secondary endpoints

| Secondary endpoints | With post-paracentesis circulatory dysfunction | Without post-paracentesis circulatory dysfunction | <i>p</i> |
|---|--|---|----------|
| Time for first readmission (mean in months) | 1.3 | 3.5 | 0.03 |
| Survival (mean in months) | 9.3 | 16.9 | 0.01 |

Discussion

The study demonstrated that post-paracentesis circulatory dysfunction did not resolve spontaneously but persisted during F/U. Among the three plasma expanders investigated, 20% albumin was least frequently associated with circulatory dysfunction. Although the number of patients studied was inadequate to detect significant differences in clinical endpoints between the groups, subgroup analysis confirmed that circulatory dysfunction was associated with poor clinical outcome during F/U. Circulatory dysfunction is characterized by marked activation of natriuretic systems and accentuated renal sodium retention, leading to rapid re-accumulation of ascites. Post-paracentesis circulatory dysfunction was also an independent predictor of survival. (See Tables 8.12 and 8.13.)

Problems

- The majority of guidelines recommend therapeutic paracentesis in patients with refractory (diuretic-resistant or diuretic-intolerant) ascites. In this study, patients with tense ascites were recruited, irrespective of the response to diuretic therapy;
- There were no significant differences in clinically important endpoints between the treatment groups. The study was powered to detect differences in post-paracentesis circulatory dysfunction between the treatment groups.

Ulcerative colitis: ciclosporin

Randomized, double-blind comparison of 4mg/kg versus 2mg/kg intravenous cyclosporine in severe ulcerative colitis.

AUTHORS: Van Assche G, D'Haens G, Noman M *et al.*

REFERENCE: *Gastroenterology* (2003) 125, 1025–31.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Intravenous low-dose (2mg/kg) ciclosporin is as effective as high-dose (4mg/kg) in the treatment of acute severe ulcerative colitis.

Impact

Since the first report of its efficacy in 1990, ciclosporin therapy has remained the only alternative to colectomy in patients with acute severe colitis who fail to respond to intravenous corticosteroids. Lower-dose therapy has the potential to reduce adverse effects and widen the use of ciclosporin therapy in these patients.

Aims

IV corticosteroids remain the mainstay of treatment for acute severe flares of ulcerative colitis (UC). However, in non-responders, IV ciclosporin had been demonstrated to be an alternative to colectomy. The first placebo-controlled trial of IV ciclosporin in acute severe colitis, as well as several uncontrolled trials, had used a starting dose of 4mg/kg over the first 24h. A lower dose of ciclosporin had also previously been used successfully in solid organ transplantation. This trial aimed to evaluate the additional clinical benefit of 4mg/kg over 2mg/kg of IV ciclosporin dose in the treatment of acute severe UC.

Methods

Patients: 73 patients at a single centre in Belgium.

Inclusion criteria: Consecutive patients admitted for acute severe UC:

- Age 18–70y;
- Lichtiger clinical activity index ≥ 10 .

Exclusion criteria:

- Serum creatinine $>2\text{mg/dL}$;
- Serum cholesterol $<150\text{mg/dL}$;
- Uncontrolled HTN;
- Positive stool culture or *Clostridium difficile* toxin.

Groups: Both groups received continuous IV infusion of ciclosporin, and blood ciclosporin levels were maintained at 250–350ng/mL in the '4mg/kg' group and at 150–250ng/mL in the '2mg/kg' group:

- 4mg/kg ($n = 38$);
- 2mg/kg ($n = 35$).

Primary endpoint: Proportion of patients with a clinical response.

Secondary endpoints:

- Time to response;
- Colectomy rates;
- Adverse effects.

Follow-up: Response assessed on d8, and colectomy rates on d14.

Results

Table 8.14 Summary of results

| Primary endpoint | 4mg/kg | 2mg/kg | p |
|----------------------------------|----------|----------|-------|
| Response rate | 84.2% | 85.7% | ns |
| Secondary endpoints | | | |
| Median time to response | 4 (1–7)d | 4 (1–8)d | ns |
| Colectomy rate within 14d | 13.1% | 8.6% | ns |
| New diastolic HTN | 23.7% | 8.6% | <0.08 |
| 10% increase in serum creatinine | 18.4% | 17.1% | ns |
| N eurotoxicity | 7.9% | 5.7% | ns |

Discussion

The value of ciclosporin therapy in acute severe UC is widely accepted, but concerns regarding toxicity have limited its use. Because most of the adverse effects of ciclosporin are dose-dependent, it is logical to recommend the lowest effective dose for treatment. This study showed that a higher dose of ciclosporin did not add any clinical benefit. Although no statistically significant difference in the frequency of adverse events was seen between the groups, this was likely to be due to a type 2 error. A trend towards the development of diastolic HTN was seen in the high-dose group. The blood levels of the drug were significantly different between the two groups, so it is logical to presume that, if the sample size were bigger, a lower dose would have been shown to be less toxic. (See Table 8.14.)

Problems

- Only half of the patients in both groups were on concomitant corticosteroid therapy. Despite the evidence for the efficacy of ciclosporin as monotherapy, it is still reserved for steroid-non-responsive patients in most centres;
- The sample size was too small to demonstrate the difference in adverse events between the two groups.

Crohn's disease: infliximab

Infliximab for the treatment of fistulas in patients with Crohn's disease.

AUTHORS: Present D, Rutgeerts P, Targan S *et al.*

REFERENCE: *N Engl J Med* (1999) **340**, 1398–405.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Infliximab is effective for the treatment of fistulae in patients with severe Crohn's disease.

Impact

Infliximab and other biological agents are increasingly used in the management of patients with severe active Crohn's disease, particularly when the disease has proven refractory to treatment with corticosteroids and other immunomodulating drugs. Infliximab maintenance therapy is now an established treatment for fistulizing Crohn's disease and selected patients without fistulae.

Aims

Enterocutaneous and perianal fistulae are common complications of Crohn's disease (CD) and are difficult to treat. Medical treatments had otherwise proven ineffective, whereas surgery usually involved the formation of stomas—undesirable to most patients. Following reports that infliximab, a genetically constructed IgG1 murine–human chimeric monoclonal antibody against TNF- α , was safe and effective in the treatment of refractory CD, this double-blind, placebo-controlled trial was specifically designed to evaluate the efficacy of infliximab in healing established enterocutaneous fistulae.

Methods

Patients: 94 patients from multiple centres in the USA and Europe.

Inclusion criteria:

- Age 18–65y;
- Single or multiple abdominal or perianal fistulae of ≥ 3 mo duration, as a complication of CD.

Exclusion criteria:

- Concurrent treatment with ciclosporin;
- Other complications of CD (e.g. current strictures or abscesses);
- No recent surgery or stoma formation (within previous 6mo);
- Previous treatment with infliximab or known allergy to murine proteins.

Groups

- IV infliximab (5mg/kg at wk 0, 2, and 6) ($n = 31$);
- IV infliximab (10mg/kg at wk 0, 2, and 6) ($n = 32$);
- Placebo ($n = 31$).

Primary endpoint: Reduction of $\geq 50\%$ in the number of draining fistulae at two consecutive visits.

Secondary endpoints:

- Complete response (absence of any draining fistulae);
- Duration of response;
- Measures of disease activity;
- Incidence of adverse events.

Follow-up: Clinical and laboratory assessments at wk 2, 4, 10, 14, and 18.

Results

Table 8.15 Summary of results

| Primary endpoint | 5mg/kg | 10mg/kg | Placebo |
|---------------------------------|--------|---------|---------|
| At least 50% response | 68%* | 56%* | 26% |
| Secondary endpoints | | | |
| Complete response | 55%* | 38%* | 13% |
| Duration of response (median) | 84d | 99d | 86d |
| Disease activity (median score) | 108% | 111% | 171% |
| Adverse events (any) | 65% | 84% | 65% |

* Statistically significant difference from placebo ($p < 0.05$).

Discussion

Infliximab is a monoclonal antibody against TNF- α , a cytokine implicated in the pathogenesis of various chronic inflammatory conditions, including CD and rheumatoid arthritis. These data suggested, for the first time, that infliximab was effective not only in achieving remission in patients with severe refractory CD (as shown in previous studies), but also in healing CD-related enterocutaneous and perianal fistulae. The larger (306 patients across 45 centres) ACCENT II trial (*N Engl J Med* (2004) **350**, 876–85) confirmed these findings and demonstrated that infliximab infusion every 8wk was effective in keeping CD fistulae dry over a period of 1y, leading to an improved QoL. Those who lose response during maintenance therapy with 5mg/kg of infliximab may respond to 10mg/kg. (See Table 8.15.)

Problems

- The median duration of response after three doses of infliximab was ~ 3 mo. Subsequent trials have shown that repeated doses can maintain fistula healing for longer periods of time;
- Although no serious adverse events were reported, concerns have been raised about the possibility of serious infection, autoimmune reaction, and even carcinogenesis associated with infliximab. Careful monitoring of patients and auditing of adverse reactions is essential;
- Infliximab is expensive; this study was not designed to evaluate its cost-effectiveness. Future studies should also include economic analyses;
- Only patients with CD were recruited. However, subsequent studies have demonstrated the efficacy of infliximab in the management of UC.

Hepatitis C: peginterferon and ribavirin

Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C.

AUTHORS: Manns M, McHutchison J, Gordon S *et al.*

REFERENCE: *Lancet* (2001) **358**, 958–65.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The combination of peginterferon and ribavirin is the most effective therapy for chronic hepatitis C. The benefit of this combination is most significant in patients with genotype 1 infections.

Impact

The addition of the polyethyleneglycol molecule to IFN allowed more convenient once-weekly dosing, making treatment more acceptable to patients. Peginterferon also contributed to a significant increase in sustained virological response (SVR) rates, in particular for genotype 1 infection, otherwise the least responsive genotype. Combination of peginterferon and ribavirin has replaced the conventional IFN-based treatment for chronic hepatitis C.

Aims

The most effective initial therapy for patients with chronic hepatitis C virus (HCV) infection had been demonstrated to be a combination of IFN α -2b plus ribavirin. Pegylation produces a biologically active molecule with a longer half-life and more favourable pharmacokinetics. This study aimed to assess the safety and efficacy of two different regimens of peginterferon α -2b plus ribavirin vs conventional IFN α -2b plus ribavirin.

Methods

Patients: 1,530 patients at 62 centres in Europe, Canada, Argentina, and the USA.

Inclusion criteria: Previously untreated chronic hepatitis C:

- HCV RNA detectable in serum by polymerase chain reaction (PCR);
- Liver biopsy within 1y consistent with chronic hepatitis;
- Elevated alanine aminotransferase.

Exclusion criteria:

- Low Hb, white blood cell (WBC) count, platelet count;
- Decompensated cirrhosis, raised α -fetoprotein, previous transplantation;
- Human immunodeficiency virus (HIV) infection;
- Pre-existing psychiatric disease, seizure disorders.

Groups:

- High-dose peginterferon: Peginterferon α -2b 1.5 micrograms/kg/wk plus ribavirin 800mg/d ($n = 511$);
- Low-dose peginterferon: Peginterferon α -2b 1.5 micrograms/kg/wk for 4wk, followed by 0.5 micrograms/kg/wk, plus ribavirin 1,000–1,200mg/d ($n = 514$);
- IFN: IFN α -2b 3MU $3\times$ /wk plus ribavirin 1,000–1,200mg/d ($n = 505$).

Primary endpoint: SVR defined as detectable HCV RNA in serum at the end of F/U.

Follow-up: Treatment was for 48wk, and patients were followed up for 24wk after the end of therapy.

Results

Table 8.16 Summary of results

| Primary endpoints | High-dose peginterferon | Low-dose peginterferon | IFN | <i>p</i> |
|--|-------------------------|------------------------|-----|----------|
| SVR at the end of treatment (all patients) | 65% | 56% | 54% | <0.001 |
| SVR at the end of F/U (all patients) | 54% | 47% | 47% | 0.01 |
| Genotype 1 | 42% | 34% | 33% | 0.02 |
| Genotype 2/3 | 82% | 80% | 79% | 0.5 |
| Genotype 4/5/6 | 50% | 33% | 38% | 0.7 |

Discussion

This large RCT demonstrated that combination of high-dose peginterferon and ribavirin treatment significantly increased the SVR rates, compared with a conventional IFN-based regime. In this study, the SVR reported with the conventional IFN group was higher than expected. Despite this, peginterferon-based treatment was clearly superior. In addition, SVR was associated with a decrease in hepatic inflammation on liver biopsy. The benefit of high-dose peginterferon was most apparent in those with genotype 1 infection, which generally responds poorly to antiviral therapy. The SE profiles were similar between groups. As compliance is a major factor in determining SVR rates in these patients, ease of once-weekly injection of peginterferon is a distinct advantage. (See Table 8.16.)

Problems

- All patients were treated for 48wk, so the efficacy of a shorter duration of treatment in genotypes 2 and 3 patients could not be evaluated;
- Peginterferon α -2b-based treatment did not lower the frequency of adverse reactions.

Chronic hepatitis C: triple therapy

Telaprevir in previously untreated chronic hepatitis C virus infection.

AUTHORS: Jacobson I, McHutchison J, Dusheiko G *et al.*

REFERENCE: *N Engl J Med* (2011) **364**, 2405–16.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Addition of telaprevir, a protease inhibitor, to pegylated interferon α and ribavirin results in significantly higher rates of sustained virological response in chronic hepatitis C virus genotype 1 infection, when compared with peginterferon–ribavirin as a standalone regime.

Impact

Triple therapy for chronic hepatitis C has achieved a step change in the efficacy of antiviral therapy, particularly in hepatitis C virus genotype 1 infection. Together with other trials, this study has revolutionized the treatment of hepatitis C viral infection. Triple therapy regimes, using either boceprevir or telaprevir, are currently recommended as first-line treatment by the UK's National Institute for Health and Care Excellence.

Aims

HCV infection is a leading cause of chronic liver disease worldwide. Associated complications, such as portal HTN and hepatocellular carcinoma, confer significant morbidity and mortality risk to chronically infected individuals. Standard antiviral therapy for chronic hepatitis C has, until recently, comprised pegylated interferon α and ribavirin, resulting in an SVR for only 40–50% of patients with genotype 1 infection. Phase 2 trials have indicated that addition of an NS3/4A serine protease inhibitor telaprevir can significantly improve SVR rates. This phase 3 RCT aimed to evaluate the safety and efficacy of a telaprevir-based triple therapy regime in previously untreated patients with chronic genotype 1 infection.

Methods

Patients: 1,095 patients from 123 international sites.

Inclusion criteria:

- Aged 18–70y;
- Chronic HCV genotype 1 infection;
- HIV-negative and hepatitis B-negative;
- Neutrophil count $>1.5 \times 10^9/\text{L}$, platelet count $>90 \times 10^9/\text{L}$, Hb $>13\text{g/dL}$ (men) or 12g/dL (women).

Exclusion criteria:

- Decompensated liver disease;
- Liver disease of a different aetiology;
- Hepatocellular carcinoma.

Groups:

- PR: Placebo with peginterferon–ribavirin for 12wk, followed by 36wk of peginterferon–ribavirin ($n = 361$);
- T8PR: Telaprevir with peginterferon–ribavirin for 8wk and placebo with peginterferon–ribavirin for 4wk, followed by 12 or 36wk of peginterferon–ribavirin on the basis of the same HCV RNA criteria ($n = 364$);
- T12PR: Telaprevir, combined with peginterferon alfa-2a and ribavirin, for 12wk, followed by peginterferon–ribavirin alone for 12wk if HCV RNA was undetectable at wk 4 and 12, or for 36wk if HCV RNA was detectable at either time point ($n = 363$).

Primary endpoint: Proportion with undetectable HCV RNA 24wk after treatment.

Secondary endpoints: Proportion with undetectable HCV RNA at wk 4 and 12, and end of treatment.

Results

Table 8.17 Summary of results

| Primary endpoint | T12PR ($n = 363$) | T8PR ($n = 364$) | PR ($n = 361$) |
|---|---------------------|--------------------|------------------|
| Undetectable HCV RNA at 24wk after end of treatment (SVR) | 271 (75%) | 250 (69%) | 158 (44%) |
| Secondary endpoints: | | | |
| Undetectable HCV RNA at wk 4 and 12 | 212 (58%) | 207 (57%) | 29 (8%) |
| Undetectable HCV RNA at end of treatment | 314 (87%) | 295 (81%) | 229 (63%) |

Discussion

Compared to a standard treatment regime of peginterferon and ribavirin for 48wk, a triple therapy regime, including telaprevir, for either 12 or 8wk, followed by a standard regime, results in significantly improved SVR rates. Over 50% of patients taking telaprevir had undetectable HCV RNA at wk 4 and 12 of treatment, suggesting that a shorter duration of treatment (i.e. from 48 to 24wk) may be adequate in this group. Patients treated for 12wk had higher SVR rates and decreased risk of virological failure, compared to those treated for 8wk. (See Table 8.17.)

Problems

- An increased incidence of SEs was observed in the telaprevir groups, including anaemia, rash, and GI disturbance;
- Patient cohorts with difficult-to-treat disease (e.g. Afro-Caribbean patients or those with advanced fibrosis) were not separately analysed for SVR in response to telaprevir-containing regimes.

Genitourinary medicine

- Introduction 242
- Syphilis: antibiotic treatment 244
- Gonorrhoea: antibiotic resistance 246
- Chlamydia: antibiotic treatment 248
- Cervical cancer: human papillomavirus vaccine 250
- Genital warts: immunomodulator cream 252
- Genital herpes simplex: antiviral therapy 254
- Genital herpes: prevention of outbreaks 256
- Pelvic inflammatory disease: inpatient vs outpatient treatment 258
- Bacterial vaginosis: antibiotic treatment 260

Introduction

The name 'genitourinary medicine' replaced venereology in the UK 32y ago. What used to be called venereal disease (VD) in the nineteenth and twentieth centuries referred to syphilis, gonorrhoea, and chancroid—still the legally defined VD. The devastating effect of syphilis on the British army (33% of sick cases) prompted government legislation (the Contagious Diseases Act 1864) to force prostitutes to be examined for VD and admitted to Lock hospitals for treatment. Meanwhile, 'normal' hospitals shunned VD. After widespread protests against its iniquity, the Act was repealed in 1886. Lobbying by various interested medical, social, and feminist campaigners produced a Royal Commission enquiry from 1913 to 1916, followed, in 1917, by the development of public services which were free, confidential, and open to anyone.

Despite the success of the VD service and subsequent incorporation into the UK's NHS, sexually transmitted disease (STD) clinics, venereologists, and those affected by STD continued to be stigmatized. The name 'genitourinary medicine' was chosen to minimize the stigma and to reflect changing epidemiology, as STDs with genitourinary manifestations overshadowed the legally defined VDs. Elsewhere, the specialty is part of dermatovenereology or other disciplines such as infectious diseases. In the UK, the continued rise in sexually transmitted infections remains a key public health concern.

Since the advent of HIV infection, many genitourinary medicine specialists have also undertaken the management of HIV and acquired immune deficiency syndrome (AIDS). There has been a move towards closer links or integration with contraception/family planning under the umbrella of sexual health. Advances in diagnostic technology, such as the recent nucleic acid amplification tests for gonorrhoea, continue to make this specialty as fascinating and satisfying as ever, combining the science of medicine with the art of clinical practice.



Syphilis: antibiotic treatment

Doxycycline compared with benzathine penicillin for the treatment of early syphilis.

AUTHORS: Ghanem K, Eberding E, Cheng W *et al.*

REFERENCE: *Clin Infect Dis* (2006) **42**, 45–9.

STUDY DESIGN: Case control study.

EVIDENCE LEVEL: 3.

Key message

Doxycycline (100mg bd for 14d) is an effective treatment for early syphilis.

Impact

The results of this study support the use of an oral regimen for treatment of early syphilis as an alternative to parenteral penicillin.

Aims

Although doxycycline was considered the preferred second-line treatment of syphilis, there had been no controlled trial data of its efficacy. Previous observational studies on small numbers of patients had shown >90% response to doxycycline treatment, and data published in the 1950s had demonstrated the efficacy of chlortetracycline and oxytetracycline. This study aimed to provide more substantial evidence for the use of a 2wk oral doxycycline (100mg bd) regime.

Methods

Patients: Retrospective study of patients treated for 1°, 2°, or early latent syphilis between October 1993 and June 2000 at two public STD clinics in the USA. Study patients drawn from a total of 1,558 patients treated with either doxycycline (100mg bd PO for 14d) or a single dose of benzathine penicillin G (BPG, 2.4MU IM).

Inclusion criteria:

- Diagnosed using the Centre for Disease Control (USA) criteria;
- Age ≥ 18 y;
- Reactive rapid plasma reagin (RPR) test (a serological, non-treponemal test to look for antibodies) confirmed by reactive fluorescence treponemal antibody absorption test before treatment;
- Clear documentation of complete treatment;
- Documented treponemal serology results at the time of treatment and ≥ 1 F/U serology titre 270–400d after treatment.

Groups:

- Doxycycline ($n = 34$);
- BPG ($n = 73$).
- Demographic/clinical features evenly distributed: 56% ♀; 98% black; 45% symptomatic; 28% contacts of syphilis; 32% (group 1) and 19% (group 2) early latent; 6% (group 1) and 13% (group 2) HIV-positive; 85% with RPR $>1:16$.

Primary outcome: Serological response (failure defined as the lack of 4-fold drop in RPR titre 270–400d after treatment or a 4-fold increase in RPR titre 30–400d after treatment, without evidence of re-infection on the basis of health adviser records).

Secondary outcome: Time to 4-fold drop in RPR titre.

Follow-up: Until a serology titre was recorded 270–400d after treatment. Median number of serology titres recorded = 3 (doxycycline group) and 2.8 (BPG group).

Results

Table 9.1 Summary of results

| | Doxycycline (<i>n</i> = 34) | BPG (<i>n</i> = 73) |
|--|------------------------------|----------------------|
| Serological failure (%; 95% CI) | 0 (0%, 0–10.3) | 4 (5.5%, 1.6–13.8) |
| Median time to serological response (95% CI) | 106d (75–149) | 137d (111–172) |

- No significant differences between groups in serological failure (after excluding re-infection) or time to serological response in responders;
- Two of the four failures were HIV-positive. There were no relapses. (See Table 9.1.)

Discussion

This study provided reassuring data on the efficacy of doxycycline, in comparison with BPG, in the treatment of early syphilis. These findings were consistent with previous reports from uncontrolled studies. The failure in the BPG group was consistent with the range reported in previous studies. Re-infection in these cases was not categorically excluded, despite careful study of the records.


Problems

- The 107 patients evaluated were only about 40% of all those screened to be eligible; therefore, the results may not represent the population at large. The loss to F/U is unlikely to have biased the results, as it was equal in both groups;
- Only 40% of patients treated with doxycycline and 37% of randomly selected penicillin-treated controls had F/U serological tests to enable evaluation of treatment efficacy;
- While a larger controlled trial is necessary for head-to-head comparison of doxycycline with parenteral penicillin, such a study is not feasible, because of the strong evidence available for the efficacy of parenteral penicillin regimens.

Gonorrhoea: antibiotic resistance

GRASP 2014 Report: Surveillance of antimicrobial resistance in *Neisseria gonorrhoeae*.

AUTHORS: Public Health England.

REFERENCE: *GRASP Annual Report (2014)*, via  <https://www.gov.uk/government/publications/gonococcal-resistance-to-antimicrobials-surveillance-programme-grasp-report>.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 1a.

Key message

National monitoring of patterns of antibiotic resistance in *Neisseria gonorrhoea* (gonococcus, GC) ensures that there is still effective treatment for this disease in the UK.

Impact

An annual update on GC antibiotic resistance has been produced since 2000. Extended-spectrum cephalosporins are among the last available agents to treat gonococcal infection. Continued surveillance is required to ensure appropriate treatment is prescribed to prevent gonorrhoea from becoming an untreatable disease.

Aims

Prior to the first GRASP study, reports of resistance had been ad hoc and provided limited data. By centralizing the collection of GC isolates, it became possible to determine a national demographic pattern of antibiotic resistance and thus provide appropriate information about which antibiotic to use. Intense monitoring of GC antibiotic resistance since 2000 detected an increasing resistance to fluoroquinolones, which had previously been extensively used to treat GC. In 2005, treatment was switched to the third-generation cephalosporins cefixime and ceftriaxone, but, in 2009, the GRASP report gave indications that there was a drift towards decreased susceptibility, particularly to the oral agent cefixime. This led to national treatment guidelines changing to recommend combination therapy of ceftriaxone (500mg IM) and azithromycin (1g PO) as first line in 2011, with a test of cure 2wk post-treatment. This review presented the results of the latest data collection published in 2012 relating to GC isolates in 2011.

Methods

GC isolates: 1,534 collected over 3mo.

Inclusion criteria:

- Twenty-four genitourinary medicine (GUM) clinics with 22 local microbiology laboratories;
- Any patient diagnosed with GC during the 3mo collection period (July to September 2011);
- Monitoring laboratory: Sexually Transmitted Bacteria Reference Laboratory.

Primary endpoint: Resistant antibiotic and type of resistance (i.e. plasmid or chromosomally acquired).

Secondary endpoints: Clinical characteristics of patients infected with GC (e.g. age, ethnicity, sexual behaviour, site of infection, symptoms).

Results

Table 9.2 Summary of results

| Primary endpoints | London | Non-London |
|---|-------------|-------------|
| Ceftriaxone resistance (MIC $\geq 0.125\text{mg/L}$) | 0% | 0% |
| Cefixime resistance (MIC $\geq 0.125\text{mg/L}$) | 11.9% | 9.9% |
| Azithromycin resistance | 0.6% | 0.5% |
| Ciprofloxacin resistance | 39.6% | 34.1% |
| Secondary endpoints | | |
| Gay/bisexual men | 57.9% of GC | 42.1% of GC |

MIC, minimum inhibitory concentration.

Discussion

GRASP provides data for England and Wales about both the prevalence of GC antibiotic resistance and the epidemiology of the disease. The advantage of this methodology was that it made information available about disease transmission, particularly in high-risk groups. Since the change in national guidelines in 2011, there has been a reduction in isolates resistant to cefixime, but azithromycin resistance has remained static. Cases of newly diagnosed GC increased by 25% between 2010 and 2011, likely due to increased screening and the use of more sensitive nucleic acid amplification tests. (See Table 9.2.)

Problems

- As this is an annual study only conducted over 3mo of the year, it could miss a rapidly emerging antibiotic-resistant isolate;
- A total of 49.3% of samples are from London hospitals, and this may lead to sample bias;
- Seasonal bias may have stemmed from the time period during which samples were acquired, as it is possible that characteristics of these patients are different from those who become infected at other times of the year.

Chlamydia: antibiotic treatment

A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis.

AUTHORS: Martin DH, Mroczkowski TF, Dalu Z et al.

REFERENCE: *N Engl J Med* (1992) 327, 921–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A single 1g dose of oral azithromycin is as effective as a 7d course of doxycycline in the treatment of uncomplicated genital chlamydia infection.

Impact

Single-dose oral azithromycin should be considered as first-line therapy to reduce the rates of treatment failure as a result of non-compliance with multi-dose regimens.

Aims

Traditional treatment of genital chlamydia infection with 7d multi-dose regimens of doxycycline or erythromycin is associated with high rates of non-compliance, especially among asymptomatic patients. Azithromycin, an azalide antibiotic, has good *in vitro* activity against *Chlamydia trachomatis*, with substantial bioavailability and a long tissue half-life. This trial evaluated the efficacy and safety of a single 1g dose of oral azithromycin, compared to the standard 7d course of doxycycline (100mg bd), for the treatment of uncomplicated genital tract chlamydia infection.

Methods

Patients: 457 patients from 12 centres in the USA.

Inclusion criteria: Attendees at sexual health, college student, and adolescent health, and family planning clinics:

- Age >16y;
- Positive *C. trachomatis* antigen test;
- No evidence of complicated infection (epididymitis, salpingitis);
- No systemic antibiotic therapy within 72h of enrolment.

Groups: Open-labelled, no placebo group. Antibiotics commenced 48h after examination and culture specimens for chlamydia (men—urethra; women—urethra and endocervix):

- Azithromycin (1g on d1) ($n = 237$: 85 ♂, 152 ♀);
- Doxycycline (100mg bd for 7d) ($n = 220$: 73 ♂, 147 ♀).

Primary endpoint: Bacteriological cure (negative *C. trachomatis* culture result at F/U).

Secondary endpoints:

- Complete resolution of signs and symptoms (clinical cure);
- No significant adverse effects with azithromycin.

Follow-up: At 5–11d, then at 12–20d, and finally at 31–35d.

Results

- Patients with a negative culture at initial visit were excluded from analysis of biological and clinical outcomes (hence, only 141 (azithromycin) and 125 (doxycycline) patients included). (See Table 9.3.)

Table 9.3 Summary of results

| Primary endpoint | Azithromycin (n = 141) | Doxycycline (n = 125) |
|----------------------|------------------------|-----------------------|
| Bacteriological cure | 136 (96%) | 122 (98%) |
| Secondary endpoints | | |
| Clinical cure—4 | 97% | 91% |
| ♀ | 98% | 95% |
| Adverse SEs | 41/237 (17%) | 43/220 (20%) |

Discussion

A previous study had demonstrated 98% efficacy for azithromycin given as a single 1g dose against uncomplicated genital chlamydia infection. This trial, comparing that same dose to the standard doxycycline treatment, showed similar efficacy. Azithromycin was as effective as doxycycline, and its use as a first-line agent overcame the problems of non-compliance associated with multi-dose regimens. Azithromycin was well tolerated, with only occasional GI SEs (similar to doxycycline).

Problems

- Clinical cure is very subjective, and the higher rates in the azithromycin group may be related to its efficacy against organisms other than *Chlamydia*, which also cause urethritis;
- Not all patients attended the three F/U sessions. Some were only assessed at the first F/U (d5–11 after treatment), when the majority of patients who failed treatment were detected. Could this have been too soon to assess?

Cervical cancer: human papillomavirus vaccine

FUTURE II (Females United To Unilaterally Reduce Endo/Ectocervical disease) study: Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions.

AUTHORS: The FUTURE II Study Group.

REFERENCE: *N Engl J Med* (2007) 356, 1915–27.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

High-grade cervical lesions associated with human papillomavirus 16 and 18, such as cervical intraepithelial neoplasia (grades 2 and 3) and adenocarcinoma *in situ*, could be prevented by the use of a quadrivalent human papillomavirus 6/11/16/18 vaccine.

Impact

Mass vaccination of ♀ children and adolescents who have yet to be infected with human papillomavirus 16 and 18 is likely to reduce related cervical disease, including cervical carcinoma. Vaccination programmes have already been approved and are being rolled out in several countries.

Aims

Cervical cancer is the second commonest malignancy in women worldwide. It accounts for large numbers of deaths each year, particularly in developing countries that have not yet been able to effectively implement the Papanicolaou (Pap) smear screening programme (often due to its cost). Up to 70% of cervical cancers are caused by infection with human papillomavirus (HPV) 16 and 18. Prophylactic vaccines had been developed, using virus-like particles (VLPs). However, their efficacy had not been evaluated in RCTs. The aim of this trial was to demonstrate the efficacy of one such vaccine against high-grade cervical lesions attributed to HPV 16 and 18.

Methods

Patients: 12,167 women at 90 study sites in 13 countries.

Inclusion criteria:

- Women aged 15–26y;
- Not pregnant at enrolment;
- No abnormal results on Pap smear;
- Lifetime number of no more than four sexual partners.

Groups: Double-blinded study. Both groups received injections at d 1, mo 2, and mo 6:

- Quadrivalent vaccine to HPV 6/11/16/18 (with aluminium adjuvant) ($n = 6,087$);
- Placebo (containing aluminium) ($n = 6,080$).

Primary endpoint: Cervical intraepithelial neoplasia (CIN) grade 2 or 3; adenocarcinoma *in situ*; or invasive carcinoma of the cervix, with the detection of DNA from HPV 16, HPV 18, or both, in ≥ 1 of three adjacent biopsy specimens of the same abnormal cervical lesion sampled at colposcopy.

Analysis: Case ascertainment 1mo after the 3rd dose of vaccine or placebo:

- Subjects with negative results on DNA and serological testing for HPV 16 and 18 at enrolment and remained DNA-negative 1mo after the 3rd dose;
- Received all doses within 1y;
- No protocol violations (e.g. pregnancy).

Follow-up: Medical history/gynaecological examination, cervical samples for Pap testing and anogenital swabs at six sites for HPV DNA testing at first-day visit. F/U at 1 and 6mo after third injection; then at mo 24, 36, and 48. Abnormal cervical lesions referred for colposcopy.

Results

Table 9.4 Summary of results

| HPV 16/18 associated lesions (populations) | Vaccine group | Placebo group | Vaccine efficacy |
|--|---------------|---------------|------------------|
| Subjects in per protocol | 1/5,305 | 42/5,260 | 98% |
| Subjects in unrestricted | 3/5,865 | 62/5,863 | 95% |
| Subjects in intention-to-treat | 83/6,087 | 148/6,080 | 44% |

Discussion

This trial demonstrated 98% vaccine efficacy in preventing HPV 16- and 18-related high-grade cervical lesions over a 3y period. However, this was only the case in those patients who had not been previously exposed to those virus subtypes. The efficacy decreased to just 44%, when those previously exposed were included. Therefore, it is only useful as a prophylactic vaccine, and the target population should be those who have yet to become sexually active. In the short term, the vaccination appeared safe, with very few initial SEs. (See Table 9.4.)

Problems

- Only effective against HPV 16 and 18; no effect against other HPV types that can cause neoplasia (will not completely eradicate cervical carcinoma and may open a niche for other subtypes);
- Does immunity wane, and will a booster dose be required? A 15y F/U study is under way.

Genital warts: immunomodulator cream

Topical imiquimod 5% cream in external anogenital genital warts.

AUTHORS: Arican O, Guneri F, Bilgic K et al.

REFERENCE: *J Dermatol* (2004) **31**, 627–31.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Imiquimod, a novel immunomodulator, is an effective and reliable treatment for external genital warts.

Impact

Imiquimod will result in complete clearance of external genital warts in over two-thirds of patients, if used for up to 12wk. It has minimal side effects, with low recurrence rates. It is an ideal treatment in patients who have had recurrent episodes of warts and are looking for a treatment they can use safely at home.

Aims

Standard treatments for warts, including ablative methods, such as cryotherapy, electrosurgery, and chemical destruction with trichloroacetic acid and podophyllotoxin, have little impact on viral clearance and infectivity, with limited success and high recurrence rates. This study aimed to assess the effects of a novel immunomodulator imiquimod.

Methods

Patients: 45 patients (each with ≥ 5 external genital warts) from three centres in Turkey.

Inclusion criteria:

- Age >18 y;
- No wart treatment in the last 3mo (local or systemic);
- No serious systemic/immunosuppressive disorder, drug and alcohol dependence, or frequently occurring genital herpes.

Groups: Double-blind trial. Both groups applied medicament $3 \times /wk$, every other day for 12wk:

- Imiquimod 5% cream ($n = 23 \text{ ♂}, 11 \text{ ♀}$);
- Placebo (Vaseline™ cream) ($n = 9 \text{ ♂}, 2 \text{ ♀}$).

Primary endpoint: Clearance rates greater than placebo.

Follow-up: Full blood count, biochemistry, HIV, syphilis serology, and pregnancy test at 1st visit. Lesions mapped, location and duration of warts recorded. F/U monthly for 6mo, and then at the end of therapy (either at 12wk or earlier, if clearance had occurred) for re-mapping of lesions and SE assessment.

Results

Table 9.5 Summary of results

| Clearance | | 0–10% | 11–50% | 51–99% | Complete |
|-----------|---|-------|--------|--------|----------|
| Imiquimod | ♂ | — | 4.5% | 40.9% | 54.5% |
| | ♀ | — | — | — | 100% |
| Placebo | ♂ | 87.5% | — | — | 12.5% |
| | ♀ | 50% | — | 50% | — |

- Differences between placebo and treatment groups statistically significant ($p < 0.001$);
- Resolution of warts commonest wk 6–12 in the treatment group, with ♀ patients demonstrating an earlier improvement;
- Imiquimod was more effective at clearing warts in the perianal region than at other genital sites;
- SEs occurred in 55% of the treatment group (mainly erythema due to immune response associated with lesion resolution). (See Table 9.5.)

Discussion

Imiquimod 5% cream was more effective than placebo, with complete clearance rates of 69.7% vs 12.5%. However, success rates were lower than with ablative techniques. Advantages of imiquimod include a low recurrence rate (18.2%), with tolerable SEs, resulting in no patients prematurely terminating treatment—cryotherapy and surgery can be painful and leave scarring. This trial demonstrated imiquimod to be a safe and effective alternative that patients could use as a home treatment.

Problems

- Although the two groups were matched for age and duration of warts, there were low numbers of patients in the placebo group, and the ratio of ♀ to ♂ were considerably different. A higher, more equitable ratio in the placebo group may have influenced the results.

Genital herpes simplex: antiviral therapy

Valaciclovir versus acyclovir in the treatment of first-episode genital herpes infection.

AUTHORS: Fife K, Barbarash R, Rudolph T et al. (Valaciclovir International Herpes Simplex Virus Study Group).

REFERENCE: *Sex Transm Dis* (1997) **24**, 481–6.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b.

Key message

A twice-daily dose of valaciclovir, a prodrug of aciclovir, is as effective and well tolerated as the latter, given five times daily in the treatment of the first episode of genital herpes.

Impact

The results of this study have led to the introduction of a twice-daily regimen—more convenient than the five-times-daily dosing of aciclovir.

Aims

Aciclovir (ACV) had been in use for a decade as an effective and well-tolerated drug for the treatment of the first episode of genital herpes, after early RCTs had shown evidence of its efficacy. Valaciclovir (VACV), the L-valine ester prodrug of ACV, had been demonstrated to be better absorbed than ACV, with more rapid and complete metabolism to ACV. This study aimed to determine whether twice-daily VACV was more efficacious than the standard five-times-daily regimen of ACV in treating patients with first presentations of genital herpes simplex virus (HSV).

Methods

Patients: 643 patients from 54 sites (mostly student STD or family planning clinics) in the USA, the UK, and Australia.

Inclusion criteria:

- Age >18y;
- First clinical episode of genital herpes;
- Presenting within 72h of lesion onset.

Exclusion criteria:

- Pregnant or breastfeeding;
- HIV antibody-positive.

Groups: Double-blinded study:

- VACV (1g: two tablets bd) and placebo (one capsule 5×/d) for 10d ($n = 323$);
- ACV (200mg: one capsule 5×/day) and placebo (two tablets bd) for 10d ($n = 320$).

Primary endpoints: Time to healing of all lesions and duration of viral shedding.

Secondary endpoints: (see Table 9.6) Intention-to-treat (ITT) analysis of all 643 patients for primary endpoints and adverse events, and subset analysis of 605 HSV-confirmed patients for all endpoints.

Follow-up: Lesions staged as macule/papule, vesicle, ulcer, or healed. Lesion swabs for culture taken on d 1, 2, 3, 5, 7, 10, and 14, and thereafter 2× weekly (if needed) until full healing. HSV 1 and 2 antibody test on d 1 and d 14. Clinical laboratory studies at baseline, d 1, and d 7 (Hb, white and platelet cell counts, creatinine, and liver enzymes).

Results

Table 9.6 Summary of results

| Efficacy endpoints | | Median (mean) | | HR (95% CI) | p |
|------------------------------------|------|---------------|----------|------------------|--------------|
| | | VACV | ACV | | |
| Days to healing | ITT | 9 (9.2) | 9 (9.5) | 1.08 (0.92–1.27) | 0.4 |
| | HSV+ | 9 (9.3) | 9 (9.5) | 1.08 (0.91–1.27) | 0.4 |
| Duration of viral shedding, d | ITT | 3 (3.7) | 3 (4.1) | 1 (0.84–1.18) | 1.0 |
| | HSV+ | 3 (3.9) | 3 (4.3) | 1.01 (0.85–1.2) | 0.9 |
| Duration of pain, d | HSV+ | 5 (5.3) | 5 (5.3) | 1 (0.85–1.18) | 1.0 |
| Days to resolution of symptoms | HSV+ | 9 (10.9) | 9 (10.6) | 1.02 (0.85–1.22) | 0.9 |
| Proportion with new lesions at 48h | HSV+ | 0.217 | 0.241 | — | Not reported |
| Maximum no. of lesions | HSV+ | 8 (10.5) | 8 (12.1) | — | Not reported |

- **SEs:** no difference between groups—headache in 41 (VACV) and 33 (ACV); nausea in 18 (VACV) and 20 (ACV);
- **Lab tests:** no adverse changes in either group. (See Table 9.6.)

Discussion

Despite previous pharmacokinetic data showing VACV (1g bd) to produce 3× as much ACV exposure as ACV (200mg 5× daily), the clinical efficacy of the two agents in this study did not differ significantly. There was also no difference in the type, incidence, and severity of adverse events. This study, with the largest number of patients evaluated, added further evidence for the use of thymidine kinase inhibitors in the treatment of first-episode genital herpes.

Problems

- No placebo control. However, previous placebo-controlled trials had already established the efficacy of ACV;
- Study was not powered to detect <10% difference, but such a difference would be clinically insignificant.

Genital herpes: prevention of outbreaks

A meta-analysis to assess the efficacy of oral antiviral treatment to prevent genital herpes outbreaks.

AUTHORS: Lebrun-Vignes B, Bouzamondo A, Dupuy A *et al.*

REFERENCE: *J Am Acad Dermatol Med* (2007) 57, 238–46.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Oral aciclovir, famciclovir, and valaciclovir for prophylaxis against recurrent episodes of genital herpes of high clinical efficacy.

Impact

As the first meta-analysis on the topic, this study strengthens the evidence base for continuous suppressive regimens of the three antiviral agents for the prevention of genital herpes outbreaks. Implications include a positive impact on individual health-related quality of life, economic benefit, and reduced transmission at community level.

Aims

This meta-analysis aimed to compare the clinical efficacies of three oral antiviral drugs (ACV, famciclovir (FCV), and VACV), already established as suitable for prophylaxis against recurrent episodes of genital herpes.

Methods

Databases searched: Medline, EMBASE, and Cochrane controlled trials register.

Inclusion criteria:

- Placebo-controlled RCT;
- Study patients not immunocompromised or pregnant;
- No reviews or cross-over trials;
- Oral prophylactic treatment;
- Study endpoint to include the number of patients developing ≥ 1 episode of disease recurrence during the trial;
- Article in English.

Data extraction: The following items were extracted from each RCT:

- Number and characteristics (sex, mean age) of patients included;
- Frequency of recurrences chosen for inclusion;
- Treatment duration;
- Antiviral drug used, and evaluated total daily dose and regimen;
- Number of recurrence-free patients.

Statistics: The pooled estimate of the global RR of recurrence during the trials was calculated for each study, using the inversed variance-weighted RR in a fixed model. This yielded bilateral 95% CI for trials and for the meta-analysis.

Results

- Baseline:
 - 14 trials evaluated: ten ACV, two FCV, three VACV (one both ACV and VACV);
 - 6,158 patients evaluated.
- RR:
 - Significant benefit of oral ACV, FCV, or VACV (RR ranging from 0.16 to 0.73);
 - RR of developing recurrence reduced by 47% (95% CI 45–49%).
- NNT: 2.15 (95% CI 2.06–2.25).
- **Regimens:** The following regimens showed efficacy:
 - ACV: 200mg 2–5×/day, 400mg bd, or 800mg od;
 - VACV: 250mg od or bd, 500mg or 1,000mg od;
 - FCV: 125mg or 250mg bd or tds;
 - Higher doses of VACV and FCV were more effective;
 - The best regimens were ACV 200mg four times daily (qds) or 400mg bd, VACV 250mg bd or 500mg od, and FCV 250mg bd;
 - VACV 500mg od appeared to be better than FCV 250mg bd in suppression of recurrent episodes and associated viral shedding;
 - ACV 400mg bd and VACV 500mg bd were equally efficacious.
- One of the RCTs was continued as an open study for 5y after the controlled phase and reported sustained efficacy.
- **SEs:**
 - Minor/transient adverse effects, such as nausea, diarrhoea, and headache, were not significantly associated with any of the three antivirals vs placebo;
 - No serious adverse effects were attributable to these oral regimens in a long-term F/U study (up to 9y).

Discussion

This evidence, along with other studies showing improvement in genital herpes-associated psychosocial morbidity and the possible reduction in infection transmission to an uninfected partner, supports the use of prophylactic suppressive antiviral treatment against recurrent genital herpes. Long-term studies showing good tolerance are also encouraging.

Problems

- Only English language articles were included in the analysis. However, the only non-English article excluded also showed efficacy for a twice-daily ACV regimen;
- Duration of F/U in most studies was relatively short, except for one that provided long-term open-label F/U data on efficacy and tolerance;
- Data on interruption of transmission to uninfected sexual partners remain scarce.

Pelvic inflammatory disease: inpatient vs outpatient treatment

PEACH (Pelvic Inflammatory Disease Evaluation and Clinical Health) study: Effectiveness of inpatient and outpatient treatment strategies for women with pelvic inflammatory disease.

AUTHORS: Ness R, Soper D, Holley R et al.

REFERENCE: *Am J Obstet Gynecol* (2002) **186**, 929–37.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The first RCT to show similar rates of pregnancy and complications among women with mild to moderate pelvic inflammatory disease treated with a cephalosporin and doxycycline, in either the outpatient or inpatient setting.

Impact

Women presenting with mild to moderate PID can be treated as outpatients, rather than being admitted to a gynaecology ward.

Aims

A cephalosporin and doxycycline combination is effective treatment for women with mild to moderate pelvic inflammatory disease (PID). However, these women have previously been treated in hospital, despite the potential to give these two antibiotics orally in an outpatient setting. This study was designed to compare the effectiveness of outpatient and inpatient treatments in both short- and long-term management.

Methods

Patients: 831 women at 13 sites (including emergency departments (EDs), clinics, and STD units) throughout Eastern, Southern, and Central USA.

Inclusion criteria: Clinically suspected PID:

- Age 14–37y and able to attend F/U (homeless patients excluded);
- A history of pelvic discomfort for a period of ≤ 30 d;
- Pelvic organ (uterine or adnexal) tenderness on vaginal examination;
- Leucorrhoea and/or mucopurulent cervicitis and/or untreated known positive gonococcal or chlamydial cervicitis.

Exclusion criteria:

- Pregnant or fetal termination/delivery in previous 14d;
- Gynaecological surgery in previous 14d or previous hysterectomy/bilateral salpingectomy;
- Antimicrobial agent use within previous 7d;
- Allergy to study medications or vomited after antiemetic treatment;
- Suspected tubo-ovarian abscess/other condition requiring surgery.

Groups:

- Inpatient treatment: cefoxitin (second-generation cephalosporin, 2g qds IV), doxycycline (100mg bd IV for minimum 48h), then doxycycline (100mg bd PO for 14d) ($n = 409$);

- Outpatient treatment: single dose of cefoxitin (2g IM) plus probenecid (1g PO), then doxycycline (100mg bd PO for 14d) ($n = 422$).

Primary endpoints: Frequency of (and time to) documented pregnancy (i.e. positive urine/blood test (beta-human chorionic gonadotrophin, β -HCG), doctor's diagnosis, or live birth).

Secondary endpoints: Short-term: change in treatment; tubo-ovarian abscess; adverse reaction; phlebitis; tender on examination at 30d; gonorrhoea, chlamydia, or endometritis at 30d. Long-term: involuntary infertility (1y of unprotected intercourse without conception); self-reported repeat PID; hysterectomy; ectopic pregnancy; chronic pelvic pain; evidence of tubal obstruction by hysterosalpingogram (HSG).

Follow-up: At d 5 and 30; then at 3-monthly intervals in the first year; thereafter every 4 mo, until study end. Gynaecological examination, and cervical and endometrial specimens performed at the 30d visit. Subsequent F/U generally conducted by telephone.

Results

Table 9.7 Summary of results

| Primary endpoint | Inpatient | Outpatient | <i>p</i> |
|----------------------------|-----------|------------|----------|
| Pregnancy | 41.7% | 42% | 1.0 |
| Secondary endpoints | | | |
| <i>N. gonorrhoea</i> | 2.4% | 2.7% | 0.4 |
| <i>C. trachomatis</i> | 3.6% | 2.7% | 0.5 |
| Ectopic pregnancies | 0.3% | 1.0% | 0.4 |
| Tubal obstruction | 33.3% | 41.2% | 0.7 |
| Chronic pelvic pain | 29.8% | 33.7% | 0.3 |
| Involuntary infertility | 17.9 | 18.4% | 0.9 |

Discussion

Previous studies which only evaluated short-term outcomes of treating women with mild to moderate PID in an outpatient setting had shown excellent rates of microbiological cure, but varying rates of clinical cure (72–97%). This larger and longer study, which compared the short- and long-term outcomes of women treated either as inpatients or outpatients, demonstrated no significant difference between the groups. (See Table 9.7.)

Problems

- Participants were primarily recruited from inner city medical centres and therefore were mainly low-income African American women—not representative of all women who develop mild to moderate PID;
- PID is a difficult clinical diagnosis, with definitive confirmation only possible in less than two-thirds of cases. Gonorrhoea and chlamydia were excluded in the majority of women in this study (66% of outpatients and 60% of inpatients), suggesting that their symptoms either were not due to PID or were due to mild PID most likely to respond to outpatient therapy.

Bacterial vaginosis: antibiotic treatment

Vaginal clindamycin and oral metronidazole for bacterial vaginosis.

AUTHORS: Paavonen J, Mangioni C, Martin M *et al.*

REFERENCE: *Obstet Gynecol* (2000) **96**, 256–60.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Clindamycin is an effective and better tolerated alternative to metronidazole in the treatment of bacterial vaginosis, with similar cure rates.

Impact

Clindamycin is used in women with metronidazole allergy and in cases of metronidazole-resistant bacterial vaginosis. An oral preparation has been used to try to prevent preterm labour in pregnancy.

Aims

Bacterial vaginosis (BV) is a vaginal infection that may cause an offensive vaginal discharge. It is linked with pelvic infections following abortions, normal deliveries, and transvaginal hysterectomies. In pregnancy, it is associated with late miscarriages and preterm labour. Metronidazole is the standard treatment for BV. However, it has unpleasant SEs, including a disulfiram-like adverse reaction when taken with alcohol. This trial aimed to compare the effectiveness and safety of clindamycin (vaginal ovules containing 100mg clindamycin) with standard therapy (oral metronidazole) in women suffering from BV.

Methods

Patients: 233 women from 23 centres in Europe.

Inclusion criteria: Laboratory criteria of BV:

- Vaginal discharge of pH >4.5;
- Presence of clue cells on wet mount slide;
- Fishy amine odour from vaginal discharge after adding 10% potassium hydroxide (positive amine test).

Groups:

- Clindamycin (100mg ovules intravaginally for 3 consecutive days) plus placebo (capsules bd PO for 7d) ($n = 113$);
- Metronidazole (500mg bd PO for 7d) plus placebo (ovules intravaginally for 3d) ($n = 120$).

Primary endpoint: Overall clinical outcome: cure (resolution of amine odour and clue cells at F/U visit), failure, adverse effect failure (i.e. stopped treatment due to SEs), and non-assessable (i.e. insufficient data to categorize as cure or failure).

Secondary endpoints: SEs and patient evaluation.

Follow-up: At 12–16d and 28–42d after the start of treatment. A vulvo-vaginal examination was performed, with vaginal discharge described. Diagnostic tests for positive amine and clue cells were repeated.

Results

Table 9.8 Summary of results

| Primary endpoint | Clinical status | Clindamycin (n = 113) | Metronidazole (n = 120) | p |
|----------------------------|---------------------------|--------------------------|----------------------------|-----|
| 1st and 2nd F/U visit | Cured | 77 (68.1%) | 80 (66.7%) | 0.8 |
| 1st F/U visit | Cured | 98 (86.7%) | 102 (85.7%) | 1.0 |
| | Clinical failure | 13 (11.5%) | 15 (12.6%) | – |
| | Adverse effect failure | 2 (1.8%) | 2 (1.7%) | – |
| | Non-assessable | 0 | 1 | – |
| 2nd F/U visit | Cured | 85 (78.7%) | 87 (76.3%) | 0.7 |
| | Clinical failure | 23 (21.3%) | 27 (23.7%) | – |
| | Non-assessable | 5 | 6 | – |
| Secondary endpoints | | | | |
| SEs | | 21 (10.3%) | 32 (16.3%) | 0.1 |
| Patient evaluation | Cured | 83/106 (78.3%) | 90/103 (79.6%) | – |

Discussion

Other trials had also shown 3d regimens of intravaginal clindamycin to be as effective as oral metronidazole for treating BV with better tolerance. This study also showed that overall cure rates remained acceptable for both agents up to 6wk after the start of treatment. This finding is based on the number of women who were defined as cured at both F/U visits. In other studies, cure rates were calculated from the number of participants at each visit. Both agents have also been shown to be efficacious for treating BV in pregnancy, with treatment before 20wk gestation reducing the incidence of preterm birth—a complication associated with infection (*Cochrane Database Syst Rev* (2007), Issue 1). (See Table 9.8.)

Problems

- A total of 399 women were originally enrolled, but only 233 (58%) were found to be eligible after proper assessment. However, the authors claimed there were enough participants to make the study statistically viable;
- The study involved the use of ovules, a clinical preparation of clindamycin not in common use;
- Each participating centre determined instances of BV themselves, rather than using a central assessor(s). However, because some of the criteria used to diagnose BV are subjective, it is possible that some women were misdiagnosed and wrongly included (and vice versa).

Geriatric medicine

- Introduction 264
- Atrial fibrillation: warfarin therapy 266
- Falls: multifactorial intervention 268
- Falls: vitamin D 270
- Delirium in hospital 272
- Mild cognitive impairment: preventing progression 274
- Alzheimer's disease: donepezil 276
- Alzheimer's disease: memantine 278
- Alzheimer's disease: antipsychotics and cognitive decline 280
- New-onset epilepsy 282
- Assessment before care home placement 284

Introduction

The medicine of older people is plagued with manifestations of the Inverse Care Law—that those in most need of medical care are least likely to receive it. There is a prejudice that geriatric medicine is simple. Yet the reality is of routine complexity—a result not least of multiple causation, chronic fluctuating course, and attendant functional and social factors. Such complex aetiology mandates multifactorial assessments and multifactorial interventions.

Complexity sits disguised beneath a simple veneer—the predominant geriatric presentations of immobility, instability, incontinence, and cognitive impairment invite a hasty, restricted response. But outcomes are optimized only when the covert issues beneath the wrapper are considered, sought, and treated. And what outcomes! There is nothing more important to the patient, or rewarding to the doctor, than enhancing functional independence or enabling a return home.

Therapeutic responses are often dominated by apathy (non-engagement, e.g. catheterizing an undiagnosed incontinent patient), sympathy (platitudes, but feeble medicine), or antipathy (overt or covert criticism). The missing factor is empathy—in this context, the empathetic response is of diagnostic and therapeutic action. Worryingly, the former ineffectual responses are now codified in a health and social care system that emphasizes care, rather than diagnosis and cure. The epidemics of frailty and other geriatric syndromes demand the highest levels of diagnostic and therapeutic precision; yet contemporary management dogma is to keep older people out of hospital and expedite their discharge home, if that threshold is crossed.

The naïve view of disease in older people leads to the notion—often implemented—that ‘anyone can do it’. But experience—and increasingly evidence—shows that many cannot. Not all older people need the skills of a geriatrician or specialist geriatric team, but appropriate skills must either be embedded within systems managing older people, or else effective screening tools developed that enable non-specialists to recognize patients who benefit from more specialist assessment.

A further paradox is that older people as a group face the greatest burden of disease and stand to benefit most from quality research—yet there is less of it. Determining the effect of complex interventions on heterogeneous populations afflicted by complex disease is inherently difficult and is made more so by high fatality, difficult F/U, and cognitive impairment. Such ‘difficult’ patients are routinely excluded from trials that seek answers to simpler—but less common and less important—clinical questions.

Atrial fibrillation: warfarin therapy

BAFTA (Birmingham Atrial Fibrillation Treatment of the Aged) study: Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation.

AUTHORS: Mant J, Hobbs F, Fletcher K *et al.*

REFERENCE: *Lancet* (2007) 370, 493–503.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Compared with aspirin, warfarin is as safe and more effective in preventing stroke in elderly people with atrial fibrillation.

Impact

This widely applicable trial should lead to an increased uptake of warfarin, an effective stroke prevention treatment, in a population in which it has previously been underutilized.

Aims

AF is a common arrhythmia in older people and a strong risk factor for stroke. Warfarin is effective in reducing this risk, but the perceived risk of bleeding in older people had limited its use. This large study aimed to assess the efficacy of warfarin, compared with aspirin, in a 1° care population of elderly patients with AF.

Methods

Patients: 973 patients from 234 GPs in England and Wales.

Inclusion criteria:

- Age >75y;
- AF or atrial flutter on ECG within the previous 2y.

Exclusion criteria:

- Rheumatic heart disease;
- Major non-traumatic haemorrhage in the previous 5y;
- Intracranial haemorrhage;
- Oesophageal varices or recent proven peptic ulcer disease;
- Terminal illness;
- Surgery in past 3mo;
- BP >180/110mmHg.

Primary endpoint: Composite of first occurrence of fatal or non-fatal disabling stroke (ischaemic or haemorrhagic), any other intracranial haemorrhage, or clinically significant arterial embolism.

Secondary endpoints:

- Major extracranial haemorrhage;
- Other admissions to hospital with haemorrhage;
- All-cause mortality.

Follow-up: Mean F/U 2.7y.

Results

Table 10.1 Summary of results

| Primary endpoint | Warfarin (annualized no. of events) | Aspirin (annualized no. of events) | RR (95% CI) Warfarin vs aspirin |
|---|---|--|---------------------------------------|
| Stroke, other intracranial haemorrhage, or systemic embolism | 24 (1.8%) | 48 (3.8%) | 0.48 (0.28–0.80) |
| Secondary endpoints | | | |
| Major extracranial haemorrhage | 18 (1.4%) | 20 (1.6%) | 0.87 (0.43–1.73) |
| Other admissions to hospital with haemorrhage | 24 (1.8%) | 19 (1.5%) | 1.22 (0.64–2.36) |
| All-cause mortality | 107 (8.0%) | 108 (8.4%) | 0.95 (0.72–1.26) |

Discussion

Given its setting (in 1° care) and its pragmatic approach to monitoring control (patients had their INR measured and controlled according to local protocols), this trial reflects widespread 1° care practice and addressed a gap in the evidence for treatment. Physicians should now be more willing to prescribe warfarin to older people, as the benefits are clear and the risks of treatment low. Although the trial was not powered to show a difference, the low rates of haemorrhage were also reassuring. (See Table 10.1.)

Problems

Assessment of risk vs benefit in the individual patient remains difficult. Older people with AF vary enormously in their risk of ischaemic stroke (e.g. higher in those with structural heart disease or previous embolism) and their risk of haemorrhage (e.g. higher in those who fall). Although this trial saw an overall advantage of treatment, subgroups may have gained no benefit or else been harmed by warfarin.

Falls: multifactorial intervention

PROFET (PRevention Of Falls in the Elderly Trial).

AUTHORS: Close J, Ellis M, Hooper R et al.

REFERENCE: *Lancet* (1999) 353, 93–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Multidisciplinary assessment and intervention reduce disability and the risk of further trauma in older people presenting with a fall.

Impact

As a result of this study (and others that developed its findings), the UK National Institute for Health and Care Excellence recommends that all older people at risk of falls should undergo an individualized multifactorial intervention, including strength and balance training, home hazard reduction, optimization of vision, and review of medication. Specialist falls services for older people are now widely developed.

Aims

The cost of falls is high—to the individual, they represent physical and psychological trauma, loss of independence, and even death; to the health service, they include a high cost and bed occupancy. Previous management of falls had commonly focused on dealing with the injury itself. However, this approach fails to address the root of the problem. This study aimed to examine whether patients would benefit from a systematic assessment of the underlying causes and functional consequences of falls.

Methods

Patients: 397 patients at the ED of one UK teaching hospital.

Inclusion criteria:

- Patients presenting with a fall to the ED;
- Aged ≥ 65 y.

Exclusion criteria:

- Significant cognitive impairment: abbreviated mental test score (AMTS) < 7 ;
- No regular carer or not local, thereby hampering postal F/U.

Groups:

- Control: standard management (ED letter to GP who assessed or referred for specialist assessment, if considered appropriate) ($n = 213$);
- Intervention ($n = 184$);
 - Medical assessment (vision, cardiovascular and neurological status, balance, cognition);
 - Occupational therapy: home assessment and intervention visit (removal or modification of hazards, provision of equipment).

Primary endpoint: Total reported number of falls.

Secondary endpoints:

- Proportion of patients unable to go out alone;
- Serious injury from falls.

Follow-up: By postal questionnaire at 4, 8, and 12mo.

Results

Table 10.2 Summary of results

| Primary endpoint | Control (<i>n</i> = 163) | Intervention (<i>n</i> = 141) | <i>p</i> |
|----------------------------|------------------------------|-----------------------------------|----------|
| Total reported falls | 510 | 183 | 0.0002 |
| Secondary endpoints | | | |
| Able to go outside alone | 106 (65%) | 108 (77%) | 0.04 |
| Serious injury | 16 (8%) | 8 (4%) | 0.05 |

- Bidisciplinary assessment resulted in many referrals to outpatients, geriatric day hospital, the optician, or the GP (e.g. for drug modification). In only 16% of assessments was no further action required. (See Table 10.2.)

Discussion

There are myriad causes of falls in older people; each fall is usually the result of the interplay between several factors—both patient-centred ('intrinsic' factors, e.g. drugs, impaired vision, poor footwear) and environmental ('extrinsic' factors, e.g. poor lighting, trip hazards). Therefore, the most effective interventions are likely to be those that screen for multiple causes and intervene on an individual basis, depending on the relevant risk factors for each individual. Such 'individualized multifactorial intervention' is at the heart of most contemporary falls prevention programmes. Unlike this study, most protocols include a programme of muscle strengthening and balance retraining, delivered by a nurse specialist, occupational therapist, or physiotherapist.

Problems

- Although such interventions reduce falls, much less is known about their effects on fall-related injuries;
- Those with significant cognitive impairment were excluded from this study, as consent would be more difficult and recall of falls impaired. This exclusion is unfortunate, as many older people who fall have a dementia syndrome, and the combination of falls and dementia is a frequent reason for long-term institutional care. Although interventions are more challenging in people with dementia, co-morbidities which impact on falls risk are more frequent, and these individuals are likely to benefit from environmental interventions.

Falls: vitamin D

Effect of vitamin D on falls.

AUTHORS: Bischoff-Ferrari H, Dawson-Hughes B, Willett W *et al.*

REFERENCE: *JAMA* (2004) **291**, 1999–2006.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Vitamin D supplements significantly reduce falls in elderly people living at home or in care homes, in addition to their known beneficial effect on bone mineral density.

Impact

Administration of vitamin D (with calcium) to elderly people at high risk of falls is now standard practice in most specialist clinical settings, although this treatment is not prescribed routinely to all elderly people. The UK National Institute for Health and Care Excellence falls prevention guidance was unfortunately published too early to consider this meta-analysis.

Aims

Falls are common in older people and lead to injury, institutional care, and sometimes death. There are theoretical benefits of vitamin D on both bone density and muscle strength, but studies of vitamin D to prevent falls have given inconsistent results. This analysis sought to synthesize all published evidence of high quality and arrive at a conclusion of greater confidence than any single trial could achieve.

Methods

Search strategy: Systematic review of all English and non-English articles using Medline, EMBASE, and the Cochrane Controlled Trials Register. Additional contact with experts, and searches of reference lists and abstracts.

Eligible studies:

- **Design:** Double-blind RCTs;
- **Intervention:** Any type of vitamin D, compared with matching placebo;
- **Population:** Elderly people living in the community or institutional care;
- Must include a definition of a fall and how falls were ascertained.

Ineligible studies:

- Uncontrolled or observational studies;
- Studies focusing on those with alcoholism or unstable health, e.g. following acute hospitalization;
- Unacceptable methodological quality.

Primary outcome:

- RR of having ≥ 1 fall.

Results

Systematic review identified 38 potentially relevant trials. These were screened independently by three investigators. A total of 33 were excluded, according to the criteria above, leaving five studies involving 1,237 participants suitable for the primary outcome analysis. Outcomes were analysed on an ITT basis.

Data synthesis:

- Corrected pooled OR for vitamin D supplementation preventing a person from falling was 0.78 (95% CI 0.64–0.92);
- Pooled risk difference was 7% (95% CI 2–12%), giving an NNT of 15;
- The inclusion of a further five trials (trials that failed to define a fall or those in unstable patients) in the meta-analysis did not alter the study conclusions;
- Subgroup analysis demonstrated that effect size was independent of:
 - Type of vitamin D;
 - Calcium supplementation;
 - Duration of therapy or F/U.

Discussion

Falls were remarkably common, affecting 16–63% of participants in the included trials. Older people are at risk of vitamin D deficiency, due to nutritional issues and lack of exposure to sunlight. The mechanism of action of vitamin D on muscle is uncertain, but other studies have detected prompt improvements in body sway and strength. This study did not detect an effect of including calcium with vitamin D. However, other studies suggest that the beneficial effect of vitamin D is lost in those with poor dietary calcium intake. Therefore, recommended preparations include Adcal-D₃[®] or Calcichew D₃ Forte[®]; two tablets each day provide calcium 1g and cholecalciferol 800U.

Problems

- The most clinically effective dose and formulation is uncertain, as is the cost-effectiveness of targeting supplementation based on pretreatment vitamin D levels;
- Calcium preparations are often poorly tolerated. Explaining the rationale for treatment and exploring alternatives, such as dispersible tablets, may improve compliance.

Delirium in hospital

Reducing delirium after hip fracture.

AUTHORS: Marcantonio E, Flacker J, Wright R et al.

REFERENCE: *J Am Geriatr Soc* (2001) 49, 516–22.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Proactive patient assessment by specialists in elderly care reduces delirium ('acute brain failure').

Impact

This is one component of a broad spectrum of evidence which supports a geriatric approach to the acutely unwell older person, including those with hip fracture. The UK National Services Framework (NSF) for Older People states 'at least one general ward in an acute hospital should be developed as a centre of excellence for orthogeriatric practice'. Several trials have described and compared different models of orthogeriatric care. There is no single effective model, but all seek to place appropriately skilled specialists (geriatricians, surgeons, anaesthetists, nurses, and therapists) close to the patient at critical points in the care pathway. Nevertheless, implementation of this guidance is incomplete; in many UK hospitals, patients only receive reactive specialist medical care.

Aims

Delirium (often referred to as 'acute confusional state' or 'acute brain failure') is a transient global disorder of cognition and is common after hip fracture, affecting up to 50% of patients. It results from the interplay of a brain with limited cognitive reserve (or one manifesting overt dementia) and extra-cerebral factors such as drug administration, fluid depletion, pain, and an unfamiliar environment. Delirium is often severe and associated with adverse long-term cognitive and physical outcomes. This trial aimed to determine whether proactive involvement of elderly care specialists would reduce the incidence of acute brain failure.

Methods

Patients: 126 patients at the orthopaedic unit of a large tertiary hospital in the USA.

Inclusion criteria:

- Admitted emergently for surgical repair of hip fracture;
- Age >65y.

Exclusion criteria:

- Metastatic cancer;
- Life expectancy <6mo 2° to co-morbid condition(s).

Groups:

- **Reactive:** Management by an orthopaedic team, with reactive involvement of medical or geriatric specialists, if requested by the orthopaedic team ($n = 64$);
- **Proactive:** Daily assessment by a geriatrician (beginning preoperatively, where possible) with targeted recommendations based on structured protocol ($n = 62$). The most commonly applied interventions were:
 - Optimization of O_2 delivery, fluid/electrolyte balance, nutrition;
 - Treatment of pain;
 - Reduction in unnecessary medications;
 - Early mobilization;
 - Early prevention, identification, and treatment of complications.

Primary endpoint: Cumulative incidence of delirium.

Secondary endpoints:

- Cumulative incidence of severe delirium;
- Length of stay.

Follow-up: Daily assessment until discharge. No longer-term F/U. Assessor blinded to treatment allocation.

Results

Table 10.3 Summary of results

| Endpoint | Reactive | Proactive | <i>p</i> |
|------------------------------|----------|-----------|----------|
| Delirium (cumulative) | 50% | 32% | 0.04 |
| Severe delirium (cumulative) | 29% | 5 | 12% |
| Length of stay (d) | 5 | 0.02 | 0.4 |

Discussion

This study showed that multifactorial intervention, addressing basic, but important, aspects of care, results in a reduced incidence of brain failure in an at-risk population. This result has been replicated in studies from other settings. The nature of the intervention suggests that it might be delivered effectively, at least in part, by other suitably trained doctors (including surgeons) or by specialist nurses. (See Table 10.3.)

Problems

- The proactive consultation service provided advice only. Adherence to that advice by the orthopaedic team was highly variable—ranging from 32% to 100% for common interventions. Improved adherence may increase the power of the intervention;
- F/U was short-term. Impact on longer-term outcomes (including cognition, residency status, and physical dependency) is unknown. There was no financial evaluation;
- Future studies should test the application of these results to other clinical settings, and the extent to which the interventions can be optimized and delivered by other health professionals.

Mild cognitive impairment: preventing progression

Vitamin E and donepezil for the treatment of mild cognitive impairment.

AUTHORS: Petersen R, Thomas R, Grundman M *et al.*

REFERENCE: *N Engl J Med* (2005) 352, 2379–88.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Donepezil and vitamin E are not effective in preventing progression from mild cognitive impairment to Alzheimer's disease.

Impact

The prospect of dementia terrifies patients and carers, who often take empiric over-the-counter medication (e.g. vitamin E) in an attempt to prevent its onset. This trial highlighted the difficulties in the design of clinical trials in the prevention of Alzheimer's disease and the limitations of treatment. It gave clinicians and patients strong evidence that drugs currently offer no useful effect on progression.

Aims

Mild cognitive impairment (MCI) is an acquired cognitive impairment that does not interfere significantly with daily activities and therefore does not meet the diagnostic criteria for a dementia syndrome. People with MCI progress to Alzheimer's disease (AD) at a rate of 10–15% per year, although such progression is not inevitable. This study aimed to determine if treatment with vitamin E or donepezil could delay the diagnosis of AD in subjects with the amnesic form of MCI.

Methods

Patients: 769 patients from 69 centres across the USA.

Inclusion criteria: Age 55–90y with:

- Amnesic form of MCI, with significantly impaired memory;
- Clinical Dementia Rating 0.5 (i.e. very mild dementia symptoms);
- Mini-Mental State Examination (MMSE) score 24–30.

Exclusion criteria:

- Significant cerebrovascular disease (modified Hachinski score >4);
- Depression (Hamilton Depression Rating Scale >12);
- CNS infarct or infection, or focal lesions on brain scan;
- Medical or psychiatric disease that could interfere with participation;
- Restrictions on concomitant use of medication with potential adverse cognitive effects.

Primary endpoint: Development of possible or probable AD.

Secondary endpoints:

- MMSE;
- AD assessment scale (cognitive subscale);
- Global Clinical Dementia Rating;
- Mild Cognitive Impairment Activities of Daily Living Scale;
- Global Deterioration Score;
- Neuropsychological battery of tests.

Follow-up: 36mo.

Results

Table 10.4 Summary of results

| Primary endpoint | HR | 95% CI | p |
|-----------------------|------|-----------|-------|
| Donepezil vs placebo: | | | |
| 12mo | 0.42 | 0.24–0.76 | 0.004 |
| 36mo | 0.80 | 0.57–1.13 | 0.2 |
| Vitamin E vs placebo: | | | |
| 12mo | 0.83 | 0.52–1.32 | 0.4 |
| 36mo | 1.02 | 0.47–1.41 | 0.9 |

- There were no sustained differences at 3y between donepezil and placebo or vitamin E and placebo in any of the secondary outcomes. (See Table 10.4.)

Discussion

The trial showed the necessity of adequate F/U in this type of prevention trial. There were apparent benefits at 12mo that were not seen in longer-term F/U; a shorter study would have given a misleading impression of treatment efficacy. This study is best viewed as a 2° prevention trial, as substantial degenerative change is already present at the stage of MCI. Determining whether planned trials are either 1° or 2° preventative in nature will have an important effect on trial design, impacting on estimates of treatment effect, sample size, and required duration of F/U. Best evidence at present suggests that maintaining a healthy lifestyle, controlling vascular risk factors, and maintaining cognitive activity (e.g. social interaction) are more important than drug treatment.

Problems

For some patients, MCI is an interim phase on the path to dementia, but this is not true for all. Until a more robust way of distinguishing between these two groups is found (perhaps through the use of biomarkers), it will be difficult to demonstrate treatment effects in prevention trials.

Alzheimer's disease: donepezil

AD2000 study: Long-term donepezil treatment in 565 patients with Alzheimer's disease.

AUTHORS: AD2000 Collaborative Group.

REFERENCE: *Lancet* (2004) **363**, 2105–15.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Donepezil has modest clinical effectiveness and may not be cost-effective.

Impact

This was one of several trials that cast doubt on the clinical benefit and cost-effectiveness of cholinesterase inhibitors, thereby influencing the 2007 decision of the UK National Institute for Health and Care Excellence to restrict the use of these agents to patients with moderate disease (at its simplest, MMSE score of 10–20). This decision has been very controversial but was supported by judicial review.

Aims

Alzheimer's dementia is a common, irreversible brain disease, which causes progressive patient disability and carer stress, and has major economic implications for health and social services. The advent of cholinesterase inhibitors (CHEIs), including donepezil, has offered hope that an effective treatment is finally available. This trial aimed to answer several important, yet unanswered, questions: what the extent of improvement in non-cognitive symptoms of dementia is; what the optimal dose is; for how long any benefits persist; and whether this medicine is cost-effective.

Methods

Patients: 486 patients from 22 centres in the UK.

Inclusion criteria: Community-resident patients with mild to moderate AD who completed a 12wk run-in period:

- Clinical diagnosis of AD \pm vascular dementia;
- Attending a UK memory clinic;
- Living in the community, with a regular carer.

Groups:

- Donepezil, sub-randomized to either 5mg or 10mg ($n = 242$);
- Placebo ($n = 244$).

Primary endpoints:

- Entry to institutional care;
- Progression of disability, defined as loss of either 2/4 basic or 6/11 instrumental activities on the Bristol Activities of Daily Living Scale.

Follow-up: At 12wk intervals until 60wk, and then annually.

Results

Table 10.5 Summary of results

| Entry to institutional care | Donepezil | Placebo | <i>p</i> |
|-----------------------------|-----------|---------|----------|
| 1y | 9% | 14% | 0.2 |
| 3y | 42% | 44% | 0.4 |
| Progression of disability | | | |
| 1y | 13% | 19% | 0.3 |
| 3y | 55% | 53% | 0.9 |

Discussion

There remains considerable uncertainty regarding the role of CHEIs in the management of dementia. For the foreseeable future, this issue will remain unresolved. (See Table 10.5.)

Problems

- Sample size: recruitment to this trial was hugely under target, largely due to the issue of NICE guidance regarding the use of CHEIs in this patient group;
- Cost-effectiveness data: there is intense debate and controversy over interpretations of cost-effectiveness data, both for this trial and for the recent NICE review. These are highly sensitive to changes in basic assumptions, including the purchase price of CHEIs and costs of social care;
- Co-prescription: AD2000 sub-randomized participants to low-dose aspirin or aspirin avoidance, complicating the evaluation of outcomes;
- Diagnostic uncertainty: there is no diagnostic test for what is essentially a pathologically defined disease, and AD2000 recruited a sample in which many may have had vascular dementia.

Alzheimer's disease: memantine

Reisberg's study: Memantine in moderate-to-severe Alzheimer's disease.

AUTHORS: Reisberg B, Doody R, Stöffler A et al. (for the Memantine Study Group).

REFERENCE: *N Engl J Med* (2003) **348**, 1333–41.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Memantine may reduce the rate of decline in patients with moderate to severe Alzheimer's disease.

Impact

Memantine remains one of the few treatment options for patients with advanced Alzheimer's disease. However, after appraisal of this trial and two others, the UK National Institute for Health and Care Excellence concluded that the evidence base was limited, that treatment benefits appeared to be modest, and that treatment with memantine was not cost-effective.

Aims

Glutamate neurons are implicated in the cognitive and functional decline seen in AD. Memantine may protect neurons from glutamate-mediated excitotoxicity. This study aimed to determine whether memantine reduces the rate of cognitive and functional decline in the later (moderate and severe) stages of AD.

Methods

Patients: 252 community-dwelling patients referred to 32 treatment centres in the USA.

Inclusion criteria: Probable AD (by clinical diagnosis):

- MMSE score of 3–14 (i.e. moderate to severe impairment);
- Age >50y;
- Reliable caregivers;
- No clinically significant medical conditions or laboratory abnormalities.

Groups:

- Memantine: 20mg/d ($n = 126$);
- Placebo ($n = 126$).

Primary endpoints:

- Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-Plus) score at 28wk;
- Change from baseline to 28wk in Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory (ADCS-ADL).

Secondary endpoints: Other scales, including the Severe Impairment Battery (SIB), MMSE, Global Deterioration Scale (GDS), Functional Assessment Staging scale (FAST), NeuroPsychiatric Inventory (NPI), and Resource Utilisation in Dementia (RUD).

Follow-up: At randomization, and at 12 and 28wk.

Results

Table 10.6 Summary of results

| Primary endpoints (at 28wk) | Memantine | Placebo | p |
|-------------------------------|-------------|--------------|--------|
| Change in CIBIC-Plus | 4.591.1 | 4.891.1 | 0.06 |
| Change in ADCS-ADL | −3.196.8 | −5.296.3 | 0.02 |
| Secondary endpoints (at 28wk) | | | |
| Change in SIB | −4.0 ± 11.3 | −10.1 ± 13.5 | <0.001 |
| Change in MMSE | −0.5 ± 2.4 | −1.2 ± 3.0 | 0.2 |
| Change in GDS | 0.1 ± 0.5 | 0.2 ± 0.5 | 0.1 |
| Change in NPI | 0.5 ± 15.8 | 3.8 ± 16.1 | 0.3 |
| Change in FAST | 0.2 ± 1.2 | 0.6 ± 1.4 | 0.02 |

- Care required, measured by RUD score, was significantly less in the memantine group (difference = 45.8h/mo; 95% CI 10–81). (See Table 10.6.)

Discussion

There is a lack of effective treatments for the common, irreversible neurodegenerative diseases (like AD) that place a major burden on formal and informal carers. This study provided evidence that memantine reduces the rate of cognitive and functional decline with clinically meaningful effects. The same research group has also published encouraging cost-effectiveness data, but these are complex and difficult to interpret. In the UK, there has been intense scrutiny of the limited available evidence for the effectiveness and cost-effectiveness of memantine for Alzheimer's dementia—a stormy debate continues.

Problems

- Possibility of bias: the withdrawal rate was higher in the placebo group, with an overall dropout rate of almost 30%, probably due to the late stage of disease studied. However, sensitivity analysis for managing missing data demonstrated that the main result was robust.

Alzheimer's disease: antipsychotics and cognitive decline

Ballard's study: Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease.

AUTHORS: Ballard C, Margallo-Lana M, Juszczak E et al.

REFERENCE: *BMJ* (2005) 330, 874–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Quetiapine (and therefore possibly other antipsychotics) is associated with accelerated cognitive decline in Alzheimer's disease.

Impact

Antipsychotics, both typical and atypical, have been commonly used in the management of the non-cognitive/behavioural symptoms of dementia. This trial was one of several which shifted practice away from pharmacological treatment and towards behavioural interventions, and, when antipsychotics have to be used, towards their short-term use alone.

Aims

Dementia can be associated with intrusive neuropsychiatric symptoms. Treatment strategies often include an antipsychotic agent. However, these have substantial adverse effects, including parkinsonism and tardive dyskinesia. This study aimed to compare the effects of quetiapine (an atypical antipsychotic) and rivastigmine (a CHEI) on agitation and cognition in people with AD living in institutional care.

Methods

Patients: 93 patients from residential care settings in the UK.

Inclusion criteria:

- Age >60y;
- Probable or possible AD;
- Clinically significant agitation for ≥ 6 wk;
- Scores ≥ 4 on the aberrant motor behaviour or irritability scales of the NPI;
- No use of antipsychotics or CHEIs for 4wk before study entry.

Groups:

- Quetiapine ($n = 31$, of which 26 started treatment);
- Rivastigmine ($n = 31$, of which 25 started treatment);
- Placebo ($n = 31$, of which 29 started treatment).

Primary endpoint: Agitation (at 6wk).

Secondary endpoints: Cognitive function at 6 and 26wk; agitation at 26wk.

Follow-up: At 0, 6, 12, and 26wk, with Cohen–Mansfield Agitation Inventory (CMAI) and SIB.

Results

Table 10.7 Summary of results

| | Mean difference in change from baseline (95% CI) | | |
|----------------|--|---------------------------------------|----------------------------------|
| | Rivastigmine vs placebo | Quetiapine vs placebo | Rivastigmine vs quetiapine |
| To 6wk | | | |
| In CMAI | 4.1 (−4.2–12.3); $p = 0.3$ | 3.5 (−3.7–10.8); $p = 0.3$ | 0.3 (−8.0 to 8.6); $p = 0.9$ |
| In SIB | −3.5 (−13.1–6.2); $p = 0.5$ | −14.6 (−25.3 to −4.0); $p = 0.009$ | 12.0 (0.8–23.2); $p = 0.04$ |
| To 26wk | | | |
| In CMAI | 2.2 (−5.3–9.7); $p = 0.6$ | 2.0 (−4.2 to 8.3); $p = 0.5$ | −0.5 (−8.0 to 6.9); $p = 0.9$ |
| In SIB | −7.5 (−21.0–6.0); $p = 0.3$ | −15.4 (−27 to −3.8); $p = 0.01$ | 8.3 (−5.6 to 22.3); $p = 0.2$ |

Discussion

Concerns have arisen regarding the use of the atypical antipsychotics risperidone and olanzapine in people with dementia, due to increased rates of cerebrovascular death (*JAMA* (2005) 294, 1934–43), culminating in a Committee on Safety of Medicines (CSM) warning in early 2004. Quetiapine was an attractive alternative. However, this study supported the use of neither CHEIs nor atypical antipsychotics in the management of Alzheimer's-related agitation. Indeed, it provided evidence of accelerated cognitive decline with quetiapine. If antipsychotics are to be used in the management of behavioural symptoms, they should be used cautiously and for short periods. There are limited therapeutic options available for the management of dementia-related agitation. Behavioural interventions are an important approach but rely heavily on the availability of staff with time, skill, and motivation. Medical and nursing assessment to rule out simple causes of agitation (such as untreated pain, constipation, and urinary retention) is crucial. (See Table 10.7.)

Problems

- Placebo response: in the participants receiving placebo, both agitation and cognition improved a little between baseline and 6wk. This may well be due to the influence of the research project itself;
- Sample size: the study was small, raising the possibility of a type 2 error, i.e. lack of evidence of an effect when one actually exists.

New-onset epilepsy

New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine.

AUTHORS: Rowan A, Ramsay R, Collins J et al.

REFERENCE: *Neurology* (2005) 64, 1868–73.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Newer antiepileptic drugs—lamotrigine and gabapentin—are better tolerated than carbamazepine in older people with new-onset epilepsy.

Impact

Guidelines continue to reflect traditional prescribing practice, favouring the older antiepileptic drugs, e.g. carbamazepine, phenytoin, and valproate. However, prescribing practice is shifting away from the older antiepileptic drugs, supported by studies such as this, and as familiarity with newer drugs increases.

Aims

In older people, the incidence of epilepsy is much higher, but antiepileptic drugs (AEDs) are less well tolerated. Treatment is complicated by co-morbidity, polypharmacy, and altered pharmacokinetics and pharmacodynamics. This study was the first to compare two newer AEDs (lamotrigine (LTG) and gabapentin (GBP)) with a well-established drug (carbamazepine (CBZ)) that is often the drug of choice, but frequently causes serious treatment-limiting SEs.

Methods

Patients: 593 patients presenting to 18 Veteran Affairs centres in the USA.

Inclusion criteria:

- Age >60y with newly diagnosed seizures (≥ 1 in last 3mo) of any type;
- Either untreated, treated short term (<4wk), or treated longer term but at subtherapeutic levels.

Exclusion criteria:

- Taking long-term AEDs;
- Terminal illness or progressive neurological disease;
- Illicit drug use, alcoholism, severe psychiatric disease.

Groups: Dosing above (if poor seizure control) or below (if toxicity) target was permitted. Patients were withdrawn from the study, if SEs coexisted with poor control:

- CBZ: target dose 600mg/d ($n = 198$);
- GBP: target dose 1500mg/d ($n = 195$);
- LTG: target dose 150mg/d ($n = 200$).

Primary endpoint: Retention in trial for 12mo, as an indicator of efficacy and tolerability.

Secondary endpoints:

- Seizure-free retention rate (SFRR) at 1y. SFRR is an ITT measure of the proportion of patients who remain seizure-free and who were not withdrawn from the study;
- Drug toxicity.

Follow-up: Double-blind, double-dummy. At least bimonthly clinical evaluation until 12mo.

Results

Table 10.8 Summary of results

| Primary endpoint | CBZ | GBP | LTG | <i>p</i> |
|---------------------------------|-------|-------|-------|----------|
| Early termination | 64.5% | 51% | 44.2% | 0.0002 |
| Secondary endpoints | | | | |
| SFRR (1y) | 22.8% | 23.2% | 28.6 | 0.33 |
| Terminated drug due to toxicity | 31% | 21.6% | 12.1% | 0.001 |

Discussion

This study of seizures in older people is the largest to date. It reflects real clinical practice, in that patients with concurrent disease were included, and both target doses and pace of dose titration were lower than is standard for younger patients. The study provides convincing evidence of improved tolerability and similar efficacy of the newer AEDs. (See Table 10.8.)

Problems

- The low SFRR indicates that the ideal AED has yet to be identified. At 1y, 56% of patients randomized to the LTG arm remained in the trial, but only 51% of these were seizure-free. There were no significant differences in seizure-free rates between drugs;
- Subjects were enrolled after only one seizure. In older people, this may be reasonable clinical practice—adverse consequences of seizures are commoner, as are risk factors (e.g. cerebrovascular disease), and recurrence rates are higher (66–90%);
- Although generally well tolerated, LTG has some SEs which are serious but rare (e.g. skin and haematological reactions).

Assessment before care home placement

The value of specialist clinical assessment of older people prior to entry to care homes.

AUTHORS: Challis D, Clarkson P, Williamson J *et al.*

REFERENCE: *Age Ageing* (2004) **33**, 25–34.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Specialist medical (geriatric) assessment before care home placement identifies covert morbidity and reduces dependency, carer distress, and emergency service contacts.

Impact

The UK National Service Framework (NSF) for Older People advises full multidisciplinary assessment for older people at risk of long-term care, accessed via a 'Single Assessment Process'. This should facilitate comprehensive geriatric assessment that includes a medical evaluation. In practice, implementation of guidance is patchy; multidisciplinary teams often have no specialist geriatric medical component, and many assessors are untrained in the identification of the need for specialist medical assessment. Therefore, specialist clinical assessment before care home admission is far from universal.

Aims

Accurate needs assessment is essential prior to consideration of care home placement, in order to ensure that those with the greatest need are awarded places. However, disagreement had existed as to the precise criteria required of such an assessment process, leading to multiple and varied assessments by different members of the multidisciplinary team. This study aimed to evaluate the effect of additional specialist (geriatric) medical assessment at the time of consideration of care home placement.

Methods

Patients: 256 patients from two social services areas in the UK.

Inclusion criteria:

- Older people with mental or physical deterioration being considered for care home placement;
- Living at home.

Exclusion criteria:

- Emergency care home admissions; team unable to assess prior to admission;
- Terminal illness;
- Recent specialist (geriatric) medical assessment.

Groups:

- Control: Usual assessment by care manager ($n = 127$);
- Clinical: Additional domiciliary clinical assessment by experienced geriatrician or psychogeriatrician. Assessment of cognitive function, affect, and ADLs, with brief clinical examination. Report to care managers, including diagnoses, prognosis, care needs, and treatment options ($n = 129$).

Primary endpoint: Admission to care home.

Secondary endpoints:

- Service use and costs;
- Dependency and behaviour;
- Carer stress and burden.

Follow-up: Unblinded. Interview at 6mo, including assessment of cognition, mood, physical dependency, and QoL.

Results

Table 10.9 Summary of results

| | Control | Clinical | <i>p</i> |
|--|-----------|-----------|----------|
| Admission to care home, 6mo (%) | 47% | 42% | ns |
| Total NHS costs, including trial assessment (£) | 10,592 | 9,461 | 0.03 |
| Total social services costs (£) | 24,138 | 22,619 | ns |
| Change in dependency, 0–6mo (Barthel index, mean (SD)) | −6.4 (14) | −2.5 (13) | 0.04 |

Discussion

Although there was no significant reduction in overall care home admissions (both residential and nursing), there were reductions in time spent in nursing homes, contact with emergency medical services, physical functional decline, and carer stress. There was a high rate of detection of potentially treatable conditions. The intervention was valued by care managers who often lacked the detailed diagnostic and prognostic information required to assist decision-making. It is possible that the limited overall effect on care home admission concealed a greater number of occasions where clinical assessment affected decision-making—in some cases, accelerating admission (e.g. untreatable progressive disease), while, in others, delaying or averting it (e.g. treatable behavioural problems). (See Table 10.9.)

Problems

- The study was small and had limited power to detect meaningful effect. Multiple outcome measurements increase the risk of type 1 errors;
- Effective cross-professional collaborative working is essential but may be difficult to deliver where there is a culture of separate practice;
- Issues for future research include whether a similar, more structured intervention may be delivered more cost-effectively by specialist nurses, and whether there are subgroups that benefit most from specialist assessments.

Haematology

- Introduction 288
- Packed red cell transfusion threshold 290
- Platelet transfusion threshold 292
- Stroke prevention in children with sickle-cell disease 294
- Acute lymphoblastic leukaemia: bone marrow transplant 296
- Chronic myeloid leukaemia: imatinib 298
- Diffuse large B-cell lymphoma: rituximab 300
- Myeloma: thalidomide 302
- Acute promyelocytic leukaemia: retinoic acid and arsenic trioxide 304
- Myelodysplasia: azacytidine 306
- Venous thromboembolism in cancer: low-molecular-weight heparin 308
- Venous thromboembolism: oral anticoagulation 310

Introduction

One of the great British contributions to medicine has been the development of the prospective RCT as a method of assessing whether novel treatments demonstrate superiority over established therapy. This replacement of clinician preference, clinical impression, and anecdote by the design and rigorous evaluation of the results of well-designed studies has been enthusiastically embraced by haematologists the world over.

Enthusiastic adoption of RCTs by haematology is probably the consequence of a number of factors. First, the training of haematologists has always involved an understanding of the pathological and scientific processes that underlie blood disorders, engendering a rational clinical approach. Second, the treatments used in the management of haematological disorders (especially leukaemias and lymphomas) are toxic and difficult to use, involving considerable clinical expertise and expense; there is little justification here for individual clinicians dabbling with such agents. Third, the stakes are high, with poor prognosis in untreated patients and often only one chance of success.

The infrastructure originally established by the MRC to perform clinical studies in acute leukaemia has been widely replicated across various disciplines.

The studies summarized here are excellent examples of how research has influenced day-to-day clinical practice, with immense and progressive benefit to patients.

Packed red cell transfusion threshold

TRICC (Transfusion Requirements In Critical Care) study: A multi-center, randomized, controlled clinical trial of transfusion requirements in critical care

AUTHORS: Hebert P, Wells G, Blajchman M et al.

REFERENCE: *N Engl J Med* (1999) **340**, 409–17.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A restrictive transfusion strategy (Hb threshold 7g/dL) is as effective as, and possibly superior to, a liberal transfusion strategy (Hb threshold 10g/dL) in adult critical care patients without ischaemic heart disease. The restrictive strategy is associated with a reduction in the overall use of red cell transfusions.

Impact

Perhaps one of the most widely applied intensive care papers ever written. A threshold Hb concentration of 7g/dL has since become standard practice for adult critical care patients without significant co-morbidity, and is widely used in other clinical settings.

Aims

Critical care patients frequently require red cell transfusions. However, while conferring benefits, transfusions themselves are associated with risks (*N Engl J Med* (2001) **354**, 1230–6). For this reason, optimal transfusion practice for this group of patients had yet to be established. This study was designed to determine whether a restrictive approach to red cell transfusion was equivalent to a more liberal strategy.

Methods

Patients: 838 patients at 22 ICUs in Canada.

Inclusion criteria: ICU patients of age >16y, with:

- Expected stay in ICU >24h;
- Hb concentration <9.0g/dL within 72h of admission;
- Euvolaemic, with no active blood loss.

Exclusion criteria:

- Unable to receive blood, active blood loss, or chronic anaemia;
- Brain death or imminent death;
- Routine cardiac surgery.

Groups:

- Liberal: Hb concentration maintained between 10 and 12g/dL, with a threshold of 10g/dL for red cell transfusion ($n = 420$);
- Restrictive: Hb concentration maintained in the range of 7–9g/dL, with a threshold of 7g/dL for red cell transfusion ($n = 418$).

Primary endpoint: All-cause mortality in the 30d after randomization.

Secondary endpoints:

- Mortality: 60d, during hospital stay, during ICU stay;
- Length of hospital and ICU stay;
- Multiple organ dysfunction (MOD) score.

Follow-up: To 60d or death.

Results

- Overall survival curves similar, but significantly different in the subgroup with APACHE (acute physiology and chronic health evaluation) score ≤ 20 ($p = 0.02$) and in those $< 55y$ ($p = 0.02$). (See Table 11.1.)

Table 11.1 Summary of results

| | Restrictive ($n = 418$) | Liberal ($n = 420$) | p |
|----------------------------|---------------------------|-----------------------|------|
| Primary endpoint | | | |
| 30d mortality | $n = 78$ (18.7%) | $n = 98$ (23.3%) | 0.1 |
| Secondary endpoints | | | |
| 60d mortality | $n = 95$ (22.7%) | $n = 111$ (26.5%) | 0.2 |
| ICU mortality | $n = 56$ (13.6%) | $n = 68$ (16.2%) | 0.3 |
| Hospital mortality | $n = 93$ (22.2%) | $n = 118$ (28.1%) | 0.05 |
| MOD score | 10.797.5 | 11.897.7 | 0.03 |
| Length of ICU stay (d) | 11 ± 10.7 | 11.5 ± 11.3 | 0.5 |

Discussion

Although largely a negative trial, its findings were extremely important. Publication came when worldwide awareness of the hazards of transfusion was rising. It reassured clinicians that withholding red cell transfusion was, at the very least, not harmful, and possibly also of benefit in critically ill patients. A transfusion threshold of 7g/dL, combined with maintenance of Hb 7–9g/dL, was as effective as (and possibly superior to) a liberal transfusion strategy. Patients in the restrictive transfusion group also had a 54% reduction in the average number of red cell units transfused.

Problems

- Potential selection bias: 3,206 patients were eligible, but only 838/2,039 (41%) of those screened for consent agreed to participate in the study.
- Only considered adults, but similar results in unwell neonates/children.
- Ongoing debate about the optimal strategy in those with significant co-morbidity, e.g. severe heart disease. Higher threshold generally accepted.
- Barely 50% of the numbers required by the power calculation were enrolled.
- Received non-leucodepleted red blood cells (RBCs). Results might be different with current RBC products, as infusion of donor leucocytes with the red cells, or the infusion of RBCs modified by storage in the presence of leucocytes, may adversely affect outcome. The UK currently leucodepletes all blood products.

Platelet transfusion threshold

The threshold for prophylactic platelet transfusions in adults with acute myeloid leukemia.

AUTHORS: Rebulla P, Finazzi G, Marangoni F et al.

REFERENCE: *N Engl J Med* (1997) 337, 1870–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There is no increased risk of major bleeding between a prophylactic platelet transfusion threshold of 10 and $20 \times 10^9/L$ in patients undergoing remission induction therapy for acute myeloid leukaemia (AML). The lower threshold is associated with a 21.5% reduction in the number of platelet transfusions.

Impact

Other trials have confirmed these findings, and a threshold platelet count of $10 \times 10^9/L$ is now the standard of care for prophylactic platelet transfusions in patients with haematological malignancies.

Aims

The ready availability of platelet concentrates has undoubtedly made a major contribution to the development and safety of intensive treatment for haematological and other malignancies. However, platelet transfusions are associated with a number of complications and are costly. This study aimed to investigate the frequency and severity of haemorrhage in patients with AML receiving prophylactic platelet transfusions at two different thresholds of platelet counts: 10 and $20 \times 10^9/L$.

Methods

Patients: 255 patients at 21 centres in Italy.

Inclusion criteria:

- Patients with newly diagnosed AML;
- Age $>16y$;
- Receiving platelet transfusions during the first course of remission induction therapy.

Exclusion criteria:

- Acute promyelocytic leukaemia;
- 2° AML;
- Blood transfusion before diagnosis of leukaemia.

Groups:

- Control: prophylactic platelet transfusions when platelet count $<20 \times 10^9/L$ ($n = 120$);
- Restrictive: prophylactic platelet transfusions when platelet count $<10 \times 10^9/L$ or between 10 and $20 \times 10^9/L$ when temperature $>38^\circ C$ in the presence of fresh minor or major bleeding or if invasive procedures necessary ($n = 135$).

Primary endpoint: Frequency and severity of haemorrhage.

Secondary endpoints:

- Number of platelet and red cell transfusions;
- Number of patients achieving complete remission;
- Mortality.

Results

Table 11.2 Summary of results

| | Restrictive | Control | <i>p</i> |
|--|------------------|------------------|----------|
| Primary endpoints | | | |
| Patients with major bleeding episodes | $n = 29$ (21.5%) | $n = 24$ (20.0%) | ns |
| Days with major bleeding episodes | $n = 123$ (3.1%) | $n = 65$ (2.0%) | ns |
| Secondary endpoints | | | |
| Number of platelet transfusions (median/range) | 6 (1–22) | 8 (2–27) | 0.001 |
| Complete remission | $n = 76$ (56.3%) | $n = 76$ (63.3%) | ns |
| Death | $n = 18$ (13.3%) | $n = 9$ (7.5%) | ns |

Discussion

A threshold platelet count of $20 \times 10^9/L$ for prophylactic platelet transfusions in patients with bone marrow failure became accepted in the 1960s, although no clinical studies directly supported this practice. The data from this study suggested that it was safe to lower the threshold to $10 \times 10^9/L$. In doing so, the use of platelet transfusions was significantly reduced. Other trials have since confirmed these findings. (See Table 11.2.)

Problems

- In the restrictive group, 22.6% of platelet transfusions were given when the platelet count was $>10 \times 10^9/L$ due to the presence of concomitant risk factors, e.g. fever, bleeding, or invasive procedure.
- There was one fatal cerebral haemorrhage in the restrictive group, although the platelet count was $32 \times 10^9/L$ when the haemorrhage began.
- A total of 21 patients did not complete F/U and were excluded in the analysis.

Stroke prevention in children with sickle-cell disease

Prevention of a first stroke by transfusions in children with sickle cell anaemia and abnormal results on transcranial doppler ultrasonography.

AUTHORS: Adams R, McKie V, Hsu L et al.

REFERENCE: *N Engl J Med* (1998) 339, 5–11.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

We can predict which children are at higher risk of stroke, but intervention with regular transfusion can subsequently mitigate that risk.

Impact

Routine Doppler ultrasonography in children with sickle-cell disease is now the standard of care from age 2 to 16y. The cut-offs for abnormal findings, as defined by this study, are now used in clinical radiography practice to define an abnormal scan.

Aims

Children with sickle-cell disease are known to have an increased rate of stroke, though the population is extremely heterogeneous. This study aimed to determine whether regular transfusion could reduce the risk of first stroke in children with sickle-cell disease.

Methods

Patients: 130 children with sickle-cell disease (60 boys and 70 girls).

Inclusion criteria:

- Children aged 2–16y;
- Homozygous sickle-cell disease or sickle β -0 thalassaemia.

Exclusion criteria:

- History of stroke;
- Current indication for or against long-term transfusion therapy;
- Concurrent treatment that affected the risk of stroke;
- HIV seropositivity;
- Previously treated for seizures;
- Serum ferritin >500ng/mL.

Groups: All underwent transcranial Doppler ultrasonography, measuring the highest time-averaged mean blood flow velocity in the middle cerebral artery (at three points), the distal internal carotid artery, the anterior and posterior cerebral arteries, and the basilar artery. Velocities <170cm/s were considered normal; 170–200cm/s were conditional and required early

repeat; abnormal velocities were $>200\text{cm/s}$ in either the internal carotid artery or middle cerebral artery. Divided into:

- Standard care ($n = 63$);
- Transfusion ($n = 67$): Targeted to reduce baseline HbS % to $<30\%$ of total Hb within 21d, without exceeding a total Hb concentration of 12g/dL and haematocrit of 36% , measured before transfusion. Exchange or simple transfusions were allowed. Once HbS % was $<30\%$, transfusions were continued every 3–4wk.

Primary endpoint: All neurological events.

Follow-up: Trial halted 16mo before planned, due to excess morbidity in standard care arm, and all patients were offered transfusion. Overall median F/U 21.1mo.

Results

Table 11.3 Summary of results

| | Standard care ($n = 63$) | Transfused ($n = 67$) | p |
|----------------------|----------------------------|-------------------------|----------|
| Cerebral haemorrhage | 1.6% | 0% | 0.002 |
| Stroke | 17.5% | 1.5% | <0.001 |
| No. of transfusions | — | 1521 | |

Discussion

This study was landmark in the management of children with sickle-cell disease. Pilot studies in transcranial Doppler imaging had shown that children with arterial velocities $>200\text{cm/s}$ had a 40% risk of stroke within the following 3wk. The study was terminated early, due to the risk reduction demonstrated in the transfused group. Annual Dopplers are now the standard of care in the UK. (See Table 11.3.)

Problems

- Small cohort with early study termination questions generalizability; however, the stakes are high, so further studies would likely be unethical.
- Validity of velocity measurements is operator-dependent and requires a high level of training to ensure consistency.
- Regular transfusion of children has attendant risks of iron accumulation, alloimmunization, and ongoing risk of transfusion-related infection.
- The mechanism by which transfusion prevents stroke is unknown.
- Follow-on 'STOP 2' attempted to define at which point transfusions could be stopped. This was terminated early, due to an increased rate of recurrence after stopping; therefore, the commencement of transfusions is a lifelong undertaking, with significant personal/health-care burdens.
- Results can only be implemented in advanced health-care settings with good access to resources—a significant problem in developing countries.
- Subsequent reports have shown that extracranial Dopplers may be just as important at determining stroke risk—perhaps more so—as where there is extracranial vessel tortuosity or narrowing, the intracranial velocities may appear falsely normal, due to a dampening effect; this study did not measure extracranial vessel velocities.

Acute lymphoblastic leukaemia: bone marrow transplant

MRC UKALL XII/ECOG E2993: In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplant is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the international ALL trial.

AUTHORS: Rowe J, Buck G, Fielding A *et al*.

REFERENCE: *Blood* (2008) **111**, 1827–33.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Sibling allogeneic bone marrow transplant (BMT) is indicated for standard-risk patients with acute lymphoblastic leukaemia (ALL) during first complete remission (CR1). All other Philadelphia chromosome-negative patients should receive chemotherapy-based consolidation and maintenance, rather than autologous BMT.

Impact

This is now the standard for treating ALL in adults.

Aims

Treatment of ALL in children had improved considerably, with long-term survival rates of 80% being achieved. In adults, survival was considerably poorer, with survival rates of (at most) 40% for those <60y old, and <10% for those >60y old. Furthermore, the low incidence of ALL in adults had made obtaining sufficient numbers for study difficult. With the graft vs leukaemia effect having been described for adult patients, the aim of this study was to prospectively define optimal therapy for ALL in adults up to the age of 60, particularly with regard to the role of allogeneic BMT in CR1. In addition, although protracted consolidation/maintenance chemotherapy had been the mainstay of treatment (largely based upon paediatric studies), this study aimed to assess the benefits of a single autologous transplant.

Methods

Patients: 1,980 patients from multiple centres in the UK and USA.

Inclusion criteria: All patients aged 15–60y (extended to 65y from 2004), with newly diagnosed ALL.

Groups: All patients received 8wk of identical induction therapy, with response evaluated at wk 4 and 8. All in CR1 went on to treatment allocation/randomization. Intensification phase prior to transplant/consolidation:

- Philadelphia +ve: Matched unrelated donor search, if no sibling donor;
- Philadelphia –ve: With HLA-matched sibling donor, assigned to allogeneic BMT;
- Other patients: Randomized to autologous BMT or standard consolidation/maintenance chemotherapy.

Primary endpoint: Overall survival at 5y after enrolment.

Secondary endpoints: Event-free survival (EFS) and relapse risk.

Follow-up: Median F/U 4y, 11mo (range 1mo to 13y and 11mo).

Results

Table 11.4 Summary of results

| 5y data: Philadelphia –ve group | Number | Overall survival (%) | EFS (%) | Relapse (%) |
|---------------------------------|------------|----------------------|----------|-------------|
| Donor vs no donor | 388 vs 527 | 53 vs 45 | 50 vs 41 | 29 vs 54 |
| High risk | 170 vs 230 | 39 vs 36 | 38 vs 32 | 36 vs 63 |
| Standard risk | 218 vs 286 | 63 vs 51 | 59 vs 48 | 25 vs 48 |
| Auto. vs chemo. | 220 vs 215 | 37 vs 46 | 33 vs 42 | 61 vs 54 |
| Sibling allo. vs chemo. | 384 vs 418 | 54 vs 44 | 50 vs 40 | 29 vs 55 |
| High risk | 168 vs 190 | 41 vs 35 | 38 vs 31 | 36 vs 63 |
| Standard risk | 216 vs 223 | 64 vs 51 | 59 vs 47 | 24 vs 48 |

High risk = age >35y; high white cell count ($>30,000 \times 10^9/L$ for B-lineage or $>100,000 \times 10^9/L$ for T-lineage) at presentation. Philadelphia +ve patients not included in analysis.

Discussion

Philadelphia –ve patients with sibling donors who received allogeneic transplants in CR1 had improved overall survival, EFS, and relapse rates, in comparison with other treatment arms ($p < 0.05$). However, high treatment-related mortality in the high-risk group meant that benefit from allogeneic BMT was restricted to the standard-risk group. In those with no sibling donor, autologous transplantation offered no benefit over chemotherapy and was associated with a higher relapse rate ($p < 0.05$). In addition, it was found that disease monitoring after induction therapy and intensification was highly predictive of outcome in non-allograft patients (overall survival, 70% vs 22%, $p = 0.001$). (See Table 11.4.)

Problems

- The optimum management of patients over the age of 60 remains to be determined, with ongoing studies into attenuated regimens and reduced-intensity conditioning allogeneic BMT as options in such patients.

Chronic myeloid leukaemia: imatinib

IRIS (International Randomized study of Interferon and STI571): Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia.

AUTHORS: O'Brien S, Guilhot F, Larson R et al.

REFERENCE: *N Engl J Med* (2003) **348**, 994–1004.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This study demonstrates unequivocal superiority of the novel BCR-ABL tyrosine kinase inhibitor (TKI) imatinib mesylate over the best previous standard medical therapy for chronic myeloid leukaemia (CML).

Impact

Imatinib is now the treatment of choice for CML. Previous standard treatment with IFN is now redundant, and the indications for allogeneic transplant are now limited to imatinib resistance and the emergence of new cytogenetic abnormalities within the CML clones.

Aims

The Philadelphia chromosome (t(9;22) reciprocal translocation) is present in 90% of patients with CML and results in the juxtaposition of DNA sequences from *BCR* and *ABL* genes. Imatinib (Gleevec®) is an oral selective inhibitor of BCR-ABL tyrosine kinase and has been demonstrated to be highly effective in patients with CML resistant to IFN and those with advanced disease. This study aimed to compare imatinib with the then best available medical therapy of IFN and cytarabine.

Methods

Patients: 1,106 patients at 177 centres worldwide (mainly Europe and the USA).

Inclusion criteria: Patients aged 18–70y with chronic-phase CML:

- Within 6mo of diagnosis;
- Previously untreated (except hydroxycarbamide);
- Creatinine $<1.5\times$ upper limit of normal;
- Eastern Cooperative Oncology Group (ECOG) performance status <3 .

Exclusion criteria:

- Pregnant or breastfeeding;
- Serious medical co-morbidities;
- Prior haematopoietic stem cell transplantation.

Groups: Non-blinded. Groups well balanced, except for more cytogenetic abnormalities, in addition to t(9;22) in the imatinib arm (12.1 vs 7.6%). Cross-over allowed for non-responders, loss of response, or intolerance (National Cancer Institute Common Toxicity Criteria for non-haematological toxicity \geq grade 3, despite dose reductions):

- IFN (escalating dose to a target of 5MU/m²/d SC) and cytarabine (20mg/m²/d SC for 10d/mo) ($n = 553$);
- Imatinib mesylate (400mg od) ($n = 553$).

Primary endpoint: Progression-free survival.

Secondary endpoints: Haematological and cytogenetic response (complete [0% Ph-positive cells] vs partial [<35% Ph-positive cells]), safety, and tolerability.

Follow-up: Median F/U 19mo. Updated to 54mo (abstract form).

Results

- Median age 50.5y (range 18–70). (See Table 11.5.)

Table 11.5 Summary of results

| | IFN and cytarabine | Imatinib | <i>p</i> |
|-----------------------------------|--------------------|-------------------|----------|
| Primary endpoint | | | |
| Progression-free survival (1y) | 79.9% | 96.6% | <0.001 |
| Secondary endpoints | | | |
| Complete cytogenetic response | 14.5% (10.5–18.5) | 76.2% (72.5–79.9) | <0.001 |
| Major cytogenetic response (<35%) | 34.7% (29.3–40.0) | 87.1% (84.1–90.0) | <0.001 |
| Complete haematological response | 55.5% (51.3–59.7) | 95.3% (93.2–96.9) | <0.001 |
| Cross-over (n) | 318 | 11 | – |

Discussion

Imatinib was a more effective and better tolerated drug. The 60mo F/U data (published in abstract form, *N Engl J Med* (2006) **355**, 2408–17) confirmed complete and major cytogenetic response rates of 92% and 87%, respectively, with overall and progression-free survivals of 89% and 83%, respectively. Outcomes were better in patients experiencing a complete cytogenetic response or major molecular response (>3 log reduction in BCR-ABL transcripts).

Problems

- There were very high rates of cross-over and treatment discontinuation in the IFN arm, with only 3% of patients remaining on IFN at 5y. A survival advantage for the imatinib arm is unlikely to be demonstrated.
- The high cross-over rate for IFN intolerance may underestimate the response rate in the IFN arm. However, an analysis with patients censored at cross-over for intolerance did not alter the results.
- This study did not address the question of duration of therapy. This is a current area of study, with preliminary data suggesting that up to 40% of patients achieving a deep molecular remission could safely discontinue therapy after several years—it is currently advised that this approach not be considered outside of a clinical trial.
- Newer TKIs (dasatinib, nilotinib) are completing trials to investigate whether their ability to achieve a faster, deeper molecular remission has long-term survival benefits.

Diffuse large B-cell lymphoma: rituximab

CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma.

AUTHORS: Coiffier B, Lepage E, Brière J *et al.*

REFERENCE: *N Engl J Med* (2002) **346**, 235–42.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy (R-CHOP) improves response rates and prolongs EFS in elderly patients with diffuse large B-cell lymphoma (DLBCL), without significant extra toxicity.

Impact

This was the first therapeutic use of a monoclonal antibody for a haematological malignancy. R-CHOP regime is now standard first-line chemotherapy for advanced-stage DLBCL (i.e. bulky stage II or stages III and IV disease).

Aims

DLBCL is the most frequent histological subtype of non-Hodgkin's lymphoma (NHL), accounting for 40% of new lymphoma cases. Standard CHOP chemotherapy induces complete response in only 40–50% of elderly patients, with only 35–40% overall survival. Attempts to improve this using more intensive regimens had been unsuccessful, instead leading to increased toxicity and no survival benefit. Rituximab, a chimeric IgG monoclonal antibody, targets CD20 (a surface protein occurring almost exclusively on mature B-cells), leading to lysis of malignant B-cells. Phase 2 trials had previously demonstrated efficacy and good safety profile, when used in combination with CHOP. This study aimed to be the first RCT to compare CHOP plus rituximab with CHOP alone.

Methods

Patients: 399 patients at 86 centres in France, Belgium, and Switzerland.

Inclusion criteria: Untreated DLBCL (Revised European American Classification of Lymphoid Neoplasms (REAL)/World Health Organization (WHO) classification):

- Age 60–80y;
- Stage II, III, or IV disease, with ECOG performance status 0–2 (i.e. good to fair).

Exclusion criteria:

- History of indolent lymphoma/T-cell lymphoma/concurrent malignancy;
- CNS involvement or peripheral neuropathy;

- Active medical condition preventing completion of therapy;
- Cardiac contraindications to doxorubicin;
- HIV/hepatitis B virus (HBV)-positive status.

Groups: Randomized and stratified, according to age-adjusted International Prognostic Index (IPI) score. Granulocyte colony-stimulating factor (G-CSF) added, following an episode of grade 4 or febrile neutropenia:

- CHOP (every 21d for eight cycles) ($n = 197$);
- R-CHOP (CHOP plus rituximab on d1 of each cycle, every 21d for eight cycles) ($n = 202$).

Primary endpoint: Response to chemotherapy (CR = complete response, CRu = unconfirmed CR, PR = partial response, SD = stable disease, PD = progressive disease).

Secondary endpoints: overall survival, and EFS at 2y, and treatment-related toxicity.

Follow-up: Median F/U 24mo. CT scan to assess response.

Results

Table 11.6 Summary of results

| | CR/CR _u | PD | EFS | Overall survival |
|----------|--------------------|--------------|--------|------------------|
| CHOP | 63% | 22% | 38% | 57% |
| R-CHOP | 76% | 9% | 57% | 70% |
| <i>p</i> | 0.003 | Not reported | <0.001 | 0.007 |

- Rituximab addition reduced the risk of events by 42% (vs CHOP alone). (See Table 11.6.)

Discussion

R-CHOP showed significantly better response rates, EFS, and overall survival than CHOP alone. This benefit was seen in patients with both low- and high-risk disease and was independent of adverse risk factors. Treatment-related toxicity was similar in both groups. Grade 3/4 infusion-related reactions (chills, fever, decreased BP, bronchospasm) were seen in 9% receiving rituximab, but all disappeared after stopping/slowing the infusion. There were no associated deaths. Mean nadir neutrophil counts were slightly lower in the R-CHOP group, but this did not translate to an increase in febrile episodes or the use of more G-CSF.

Problems

- Subsequent analyses suggest the survival benefit of R-CHOP is restricted to DLBCL with BCL-2 expression, an immunohistochemical marker associated with poor prognosis and chemotherapy resistance.
- This trial considered a limited patient group (elderly with advanced disease). However, subsequent studies have confirmed the efficacy of rituximab in younger patients and in those with limited staging.

Myeloma: thalidomide

Oral melphalan and prednisolone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma.

AUTHORS: Palumbo A, Bringhen S, Caravita T et al. (GIMEMA trials group).

REFERENCE: *Lancet* (2006) **367**, 825–31.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The first RCT of thalidomide in previously untreated patients with myeloma. It was the first study to show an improvement over melphalan and prednisolone (which have been standard therapy for elderly patients with myeloma since the 1960s).

Impact

The use of novel agents, such as thalidomide, in combination with steroid, with or without alkylating agents, is now acknowledged as the preferred standard of care.

Aims

Thalidomide had been demonstrated to be effective as a single agent in relapsed myeloma, with response rates of 25–35%, increased to 50% in combination with steroid, and to 70% with the further addition of alkylating agents. This study aimed to assess the benefits of the addition of thalidomide to the previously accepted standard of melphalan and prednisolone.

Methods

Patients: 331 patients at 54 centres in Italy.

Inclusion criteria: Patients with previously untreated myeloma:

- Age >65y (or younger but unsuitable for high-dose chemotherapy);
- Salmon and Durie stages II–III;
- Measurable disease;
- Suitable candidates for high-dose therapy.

Exclusion criteria: Peripheral neuropathy.

Groups: Non-blinded:

- MP: melphalan and prednisolone (*n*: randomized = 164, F/U to >6mo = 126);
- MPT: melphalan, prednisolone, and thalidomide (*n*: randomized = 167, F/U to >6mo = 129).

Primary endpoints: Response rates (complete response, CR; partial response, PR; minimal response, MR) and EFS.

Secondary endpoints: Overall survival, time to response, and adverse events.

Follow-up: Median F/U of survivors 15.2 and 17.6mo in the MP and MPT groups, respectively.

Results

- Median age 72y (60–85). (See Table 11.7.)

Table 11.7 Summary of results

| | MP | MPT | Difference | p (95% CI) |
|--------------------------|-----------------|-----------------|------------|---------------|
| Primary endpoints | | | | |
| CR | 2.4% | 15.5% | 13% | 16.5–39.1% |
| PR | 45.2% | 60.4% | 15.2% | 3.0–26.9% |
| No change/MR | 31.8% | 10.8% | –21% | Not reported |
| Progression | 16.7% | 7.8% | –8.9 | –17.2 to –0.8 |
| EFS (at 2y) | 27% (16–22) | 54% (27–38) | 27% | 0.0006 |
| Secondary endpoints | | | | |
| Overall survival (at 3y) | 80% | 64% | –16% | 0.2 |
| Time to PR | 3.1mo (25–210d) | 1.4mo (22–200d) | –1.7mo | Not reported |

Discussion

This study demonstrated clear superiority of the addition of thalidomide to melphalan and prednisolone, with similar results in age groups greater and less than 70y of age. This benefit was achieved at the expense of greater toxicity, although the risk of thromboembolism was effectively reduced by LMWH.

Problems

- The median duration of thalidomide therapy was short (8mo).
- Thalidomide was associated with increased grade 3–4 toxicity (particularly neuropathy, infection, and VTE). The latter complication was significantly reduced by the introduction of prophylactic enoxaparin halfway through the study.
- The MPT group received thalidomide as maintenance, as well as initial, therapy. The duration of therapy was therefore longer in the MPT arm, and the relative merits of thalidomide as induction therapy vs thalidomide as maintenance therapy remain unknown. Myeloma XI is a current UK trial that aims to answer the question of whether maintenance therapy confers benefit.

Acute promyelocytic leukaemia: retinoic acid and arsenic trioxide

Retinoic acid and arsenic trioxide for acute promyelocytic leukemia.

AUTHORS: Lo-Coco F, Avvisati G, Vignetti M *et al.*

REFERENCE: *N Engl J Med* (2013) **369**, 111–21.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

All-trans-retinoic acid (ATRA) plus arsenic trioxide (ATO) shows non-inferiority to ATRA plus chemotherapy in the treatment of patients with low-to-intermediate-risk acute promyelocytic leukaemia (APML).

Impact

The first paper to show that long-term remission in APML can be induced without conventional chemotherapy.

Aims

Small single-centre pilot studies of ATO, with or without ATRA, have been shown to be highly efficacious, with reduced haematological toxicity, in newly diagnosed patients with low-to-intermediate-risk disease. This study was designed to compare the efficacy and toxicity of standard ATRA plus chemotherapy with ATRA plus ATO (i.e. without the addition of standard chemotherapy) across multiple centres.

Methods

Patients: 162 patients at 67 centres across Italy, Germany, and Austria.

Inclusion criteria:

- Age 18–71y;
- Newly diagnosed APML, confirmed at a reference laboratory;
- Low-to-intermediate risk (white cell count (WCC) $<10 \times 10^9/L$ at diagnosis);
- WHO performance score ≤ 2 ;
- Creatinine $\leq 265 \text{ mmol/L}$ and bilirubin $\leq 51 \text{ mmol/L}$.

Exclusion criteria:

- Unable to provide written informed consent;
- WCC at diagnosis $>10 \times 10^9/L$.

Groups: Non-blinded:

- ATRA + chemotherapy ($n = 79$): Induction = ATRA $45 \text{ mg/m}^2/\text{d}$ + idarubicin $12 \text{ mg/m}^2/\text{d}$ for 4d. Course 2 = + idarubicin $5 \text{ mg/m}^2/\text{d}$ for 4d. Course 3 = + mitoxantrone $10 \text{ mg/m}^2/\text{d}$ for 5d. Course 4 = ATRA $45 \text{ mg/m}^2/\text{d}$ + idarubicin $12 \text{ mg/m}^2/\text{d}$ for 1d. Maintenance = ATRA $45 \text{ mg/m}^2/\text{d}$, alternating with 6-mercaptopurine $50 \text{ mg/m}^2/\text{d}$ for 15d 3-monthly for 2y + methotrexate $15 \text{ mg/m}^2/\text{wk}$;

- ATRA + ATO ($n = 77$): Induction = ATRA $45\text{mg}/\text{m}^2/\text{d}$ + ATO $0.15\text{mg}/\text{kg}/\text{d}$ until complete remission. Consolidation = for 28wk—ATRA $45\text{mg}/\text{m}^2/\text{d}$ for 15d + ATO $0.15\text{mg}/\text{kg}/\text{d}$ for 5d/wk.

Primary endpoint: EFS at 2y after diagnosis.

Secondary endpoints:

- Rate of haematologic complete remission after induction;
- Probability of overall survival;
- Cumulative incidence of relapse;
- Toxic effects;
- Kinetics of minimal residual disease.

Follow-up: Median F/U 34.4mo.

Results

- Median age 72y (60–85). (See Table 11.8.)

Table 11.8 Summary of results

| | ATRA + chemo ($n = 79$) | ATRA + ATO ($n = 77$) | p |
|-----------------------------------|------------------------------|----------------------------|--------|
| Primary endpoint | | | |
| 2y EFS | 86% | 92% | 0.02 |
| Secondary endpoints | | | |
| Complete haematological remission | 95% | 100% | 0.12 |
| 2y overall survival | 91% | 99% | 0.02 |
| Relapse incidence | 6% | 1% | 0.24 |
| Haematological toxicity | 85% | 38% | <0.001 |
| Non-haematological toxicity | 6% | 63% | <0.001 |

Discussion

This was the first study to suggest that APML is curable without chemotherapy. They demonstrated improvement in 2y overall survival, which is perhaps reflective of reduced haematological toxicity and lower overall non-leukaemic mortality.

Problems

- More hepatic toxicity in the ATRA-ATO arm.
- Only valid in patients with low-to-intermediate-risk APML.
- Risk of QT_c prolongation with ATO—led to discontinuation and treatment off study in one patient.
- ATO can only be delivered in a few UK hospitals, due to strict handling procedures and limited supply.

Myelodysplasia: azacytidine

Efficacy of azacytidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study.

AUTHORS: Fenaux P, Mufti G, Hellstrom-Lindberg E *et al.*

REFERENCE: *Lancet* (2009) **10**, 223–32.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Azacytidine can increase overall survival and reduce transfusion dependency in patients with high-risk myelodysplastic syndrome (MDS).

Impact

Azacytidine is now the 1° treatment option in high-risk MDS.

Aims

High-risk MDS are clonal disorders characterized by leukaemic transformation and cytopenias. The median survival of the highest-risk disease (intermediate-2 and high-risk) are 1.2y and 0.4y, respectively. Before this trial, there were no meaningful treatment options that offered an improvement in overall survival in such patients, other than allogeneic BMT. This study aimed to evaluate the ability of azacytidine, a chemical analogue of the cytosine nucleoside in DNA and RNA, to improve survival in high-risk MDS.

Methods

Patients: 358 at 79 sites in 15 countries.

Inclusion criteria:

- Age ≥ 18 y;
- Higher-risk MDS (International Prognostic Scoring System (IPSS) rating of intermediate-2 or high risk);
- Refractory anaemia with excess blasts (RAEB)/chronic myelomonocytic leukaemia (CMML);
- ECOG performance status 0–2;
- Estimated life expectancy of ≥ 3 mo.

Exclusion criteria:

- Therapy-related MDS;
- Previous azacytidine treatment;
- Planned allogeneic stem cell transplantation.

Groups: Non-blinded:

- Azacytidine ($n = 179$): SC injection 75mg/m²/d for 7d every 28d;
- Conventional care regimens (physician choice) ($n = 179$): Best supportive care only (including transfusions, antibiotics), low-dose cytarabine chemotherapy, intensive AML-like chemotherapy.

Primary endpoint: Overall survival.

Secondary endpoints:

- Time to transformation to AML;
- Haematological response;
- Independence from red cell transfusion;
- Number of infections requiring IV antibiotics;
- Occurrence of adverse effects.

Follow-up: Median F/U 21.1mo.

Results

- Median age 69y (range 38–88). (See Table 11.9.)

Table 11.9 Summary of results

| | Azacytidine (n = 179) | Conventional care (n = 179) | p |
|-------------------------------|--------------------------|--------------------------------|---------|
| Primary endpoint | | | |
| Overall survival | 24.5mo | 15.0mo | 0.0001 |
| Secondary endpoints | | | |
| Time to transformation to AML | 17.8mo | 11.5mo | <0.0001 |
| Haematological response | 29% | 12% | 0.0001 |
| Duration of response | 13.6mo | 5.2mo | <0.0001 |
| Transfusion independence | 45% | 11% | <0.0001 |
| Infections (rates/y) | 0.60 | 0.92 | 0.0032 |
| Adverse effects | | | |
| Neutropenia | 91% | 76% | |
| Thrombocytopenia | 85% | 80% | |
| Anaemia | 57% | 68% | |

Discussion

This is the first and only drug specifically licensed in high-risk MDS shown to have a proven mortality benefit. This study has opened the door to wider investigation of the use of hypomethylating agents in MDS. Azacytidine is being successfully used to delay transformation to acute leukaemia in patients who would previously have only received supportive therapy.

Problems

- ‘Conventional care regimes’ (control group) are a heterogeneous mix of low- or high-dose chemotherapy or supportive care only.
- Interobserver variation in diagnostic features to define higher-risk MDS meant that 18 patients with lower-risk disease were enrolled in the study inappropriately.

Venous thromboembolism in cancer: low-molecular-weight heparin

Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer.

AUTHORS: Lee AYY, Levine MN, Baker RI *et al.*

REFERENCE: *N Engl J Med* (2003) **349**, 146–53.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This was the first trial exclusively conducted in patients with cancer and VTE. It showed that dalteparin, a LMWH, was more effective than oral anticoagulation at reducing the risk of recurrent thromboembolism, without increasing the risk of bleeding.

Impact

The standard of care in patients with cancer and VTE is LMWH.

Aims

Oral anticoagulation in patients with cancer can be extremely difficult to control, due to a number of factors (e.g. weight changes, dietary restrictions, nausea and vomiting, poor GI absorption); therefore, parenteral anticoagulation had been considered a better option. Earlier trials (smaller and in non-cancer patients) had not shown a difference in recurrence rates). This study aimed to evaluate the LMWH in reducing the risk of recurrent thromboembolism.

Methods

Patients: 676 in eight countries internationally.

Inclusion criteria:

- Adult patients;
- Active cancer (other than basal cell carcinoma or SCC of the skin) diagnosed or recurred within 6mo of enrolment;
- Treatment of cancer within 6mo of enrolment;
- Newly diagnosed symptomatic proximal DVT, PE, or both (confirmed radiologically).

Exclusion criteria:

- Weight <40kg;
- ECOG performance status 3–4;
- Received therapeutic doses of any heparin for >48h before randomization;
- Already receiving oral anticoagulation therapy;
- Active or serious bleeding within previous 2wk;
- Co-morbidity associated with a significant risk of bleeding;
- Platelets <75 × 10⁹/L or creatinine level >3 × upper limit;

- Contraindications to heparin therapy;
- Pregnancy;
- Unable to return to clinical centre for F/U.

Groups: Non-blinded:

- Oral anticoagulant ($n = 338$): Warfarin or acenocoumarol, target INR 2–3;
- LMWH ($n = 338$): Dalteparin 200IU/kg body weight SC od.

Primary endpoint: First episode of recurrent, symptomatic DVT, PE, or both.

Secondary endpoints: Clinically overt bleeding (major and minor) and death.

Follow-up: 6mo.

Results

- Median age 69y (range 38–88) (See Table 11.10.)

Table 11.10 Summary of results

| | Dalteparin ($n = 338$) | Oral anticoagulant ($n = 338$) | <i>p</i> |
|---------------------|-----------------------------|-------------------------------------|----------|
| Primary endpoint | | | |
| Recurrent VTE | 8% | 16% | 0.002 |
| Secondary endpoints | | | |
| Major bleeding | 6% | 4% | 0.27 |
| Any bleeding | 14% | 19% | 0.09 |
| Death | 38% | 40% | 0.53 |

Discussion

This trial, conducted exclusively in patients with cancer, showed a statistically significant reduction in the recurrence of VTE when patients with cancer received LMWH. There was no difference in rates of clinically significant bleeding. It should be noted that 20 of the 53 recurrent events in the oral anticoagulation population occurred when the INR was <2.0 .

Problems

- Applicability to a real-world population is limited, due to strict exclusion criteria.
- Did not include patients already established on anticoagulation; therefore, outcomes not directly applicable to those who develop cancer later and 'switch'.
- Duration of anticoagulation not well established.
- Sites and types of malignancy extremely heterogenous.
- No monitoring of efficacy of anticoagulation undertaken in the LMWH arm.

Venous thromboembolism: oral anticoagulation

Oral rivaroxaban for symptomatic venous thromboembolism.

AUTHORS: Bauersachs R, Berkowitz S, Brenner B et al.

REFERENCE: *N Engl J Med* (2010) **363**, 2499–510.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Rivaroxaban as a single drug treatment for acute symptomatic DVT, when compared to conventional therapy (SC LMWH, followed by warfarin), is non-inferior, with a favourable safety profile.

Impact

Rivaroxaban has changed the face of anticoagulation, adding more therapeutic options to treatment and providing a much needed oral alternative to warfarin for patients with DVT.

Aims

This study aimed to investigate the efficacy of rivaroxaban, an orally active direct factor Xa inhibitor, in the acute DVT setting, assessing both efficacy and safety.

Methods

Patients: 3,449 patients at multiple international centres.

Inclusion criteria:

- Legally able to consent;
- Acute, symptomatic, objectively confirmed proximal DVT;
- Absence of symptomatic PE.

Exclusion criteria:

- Treated with therapeutic doses of LMWH, fondaparinux, or UFH for >48h before randomization;
- Treated with ≥ 1 dose of a vitamin K antagonist before randomization;
- Received thrombolysis, a vena caval filter, or a fibrinolytic agent during the current episode of thrombosis;
- Any known contraindication to enoxaparin, warfarin, or acenocoumarol.

Groups: Blinded:

- Oral rivaroxaban ($n = 1,718$): 15mg bd for 3wk, followed by 20mg od for intended 3, 6, or 12mo of treatment;
- Standard therapy ($n = 1,705$): SC enoxaparin, 1mg/kg body weight bd, and either warfarin or acenocoumarol. Enoxaparin was discontinued when the INR ≥ 2.0 for 2 consecutive days and the patient had received ≥ 5 d of enoxaparin treatment. The target INR was 2.0–3.0.

Primary endpoints:

- Symptomatic recurrent VTE (DVT, or non-fatal or fatal PE);
- Clinically relevant bleeding (major and non-major).

Secondary endpoints:

- All-cause mortality;
- Vascular events (ACS, ischaemic stroke, TIA, or systemic embolism);
- Net clinical benefit (composite of reduction of recurrent VTE or major bleeding).

Follow-up: Duration of intended therapy (3, 6, or 12mo) with event-driven termination only.

Results**Table 11.11** Summary of results

| | Conventional therapy (n = 1,705) | Rivaroxaban (n = 1,718) | p |
|----------------------|-------------------------------------|----------------------------|---------|
| Primary endpoint | | | |
| Recurrent VTE | 3.0% | 2.1% | <0.0001 |
| Secondary endpoints | | | |
| Bleeding | 8.1% | 8.1% | 0.77 |
| Net clinical benefit | 4.2% | 2.9% | 0.03 |
| Vascular events | 0.8% | 0.7% | |

Discussion

The novel oral anticoagulants (NOACs) as a group have revolutionized the treatment of VTE, reducing the burden upon patients of blood tests and dietary restrictions. This study shows similar efficacy of rivaroxaban as a single agent for the acute treatment of DVT, when compared with conventional therapy. When the attendant costs and risks of vitamin K antagonist therapy are taken into account, single-agent oral therapy is a significant advancement in the treatment of symptomatic VTE. Adoption of the NOACs is rising in the UK. (See Table 11.11.)

Problems

- The NOACs have no specific reversal agents (unlike vitamin K antagonists). As there remains a risk of bleeding, this is an impediment to universal adoption as a treatment (although this study showed only a small risk of major haemorrhage—0.7%—with no fatal haemorrhages).
- Lack of monitoring means that the onus is on the patient; the NOACs remain unsuitable for patients with historic poor adherence to therapy.
- Shorter half-lives mean that one missed dose has a more significant impact with NOACs than warfarin and may contribute to the risk of recurrence.
- The results are not generalizable to all patient subgroups. In particular, there was under-representation of patients with active malignancy (only 7% in both groups).

HIV medicine

Introduction 314

Antiretroviral therapy to prevent transmission of HIV 316

Continuous vs intermittent antiretroviral therapy 318

New antiretroviral agents for treatment-experienced individuals 320

Ritonavir-boosted atazanavir vs efavirenz and comparison of two NRTI backbones 322

Combination treatment for hepatitis C in HIV-positive individuals 324

Early antiretroviral therapy in HIV-associated tuberculosis 326


Introduction

HIV/AIDS is a dynamic and fast-moving specialty. It is now over 30y since the recognition of the acquired immune deficiency syndrome in 1981, when reports were published of homosexual men in the USA presenting with unusual infections, such as *Pneumocystis* pneumonia and cytomegalovirus retinitis, and malignancies such as Kaposi's sarcoma. The cause of this syndrome, a retrovirus related to simian retroviruses, was established in 1983.

Retrospectively, it now seems likely that human infections had occurred since at least the 1930s in parts of Africa, and a phylogenetic study of human and simian retroviruses has established the zoonotic origins of HIV-1 from chimpanzees and HIV-2 from sooty mangabeys.

Early in the pandemic, mortality was high, and treatment was limited to management and prevention of opportunistic infections. With the development of effective antiretroviral therapy (ART), treatment improvements have meant that HIV has been transformed from a fatal condition to a chronic infection, with dramatic improvements in life expectancy. This change was heralded by the development of protease inhibitors and the strategy of using three drugs in combination, so-called highly active antiretroviral therapy (HAART), in 1996. More recently, combined data from international clinical trials have shown life expectancy similar to the general population among those stable on ART.¹

The outlook for people living with HIV is therefore cause for optimism. However, 34 million people are estimated to be living with HIV globally, and issues of access to, and retention in, care persist in resource-constrained settings, most notably in sub-Saharan Africa where the prevalence of HIV infection is highest. In the UK, with good access to, and retention in, care, late diagnosis is the main threat to successful treatment outcomes.²

Here we present some of the evidence that guides current practice, much of it recent, and some of it likely to be superseded in the months and years to come by newer trials and shifting paradigms. This evidence largely refers to treatment of HIV-1 infection; HIV-2 is much less prevalent globally and requires an adjusted therapeutic approach. For up-to-date UK treatment guidelines, visit the British HIV Association (BHIVA) website ( www.bhiva.org).

References

1. Rodger AJ, Lodwick R, Schechter M *et al.* (2013). Mortality in well controlled HIV in the continuous antiretroviral therapy arms of the SMART and ESPRIT trials compared with the general population. *AIDS* 27, 973–9.
2. Lucas S, Curtis H, Johnson M (2008). National review of deaths among HIV-infected adults. *Clin Med* 8, 250–2.

Antiretroviral therapy to prevent transmission of HIV

HPTN 052: Prevention of HIV-1 infection with early antiretroviral therapy.

AUTHORS: Cohen M, Chen Y, McCauley M et al.

REFERENCE: *N Engl J Med* (2011) 365, 493–505.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Successful ART is effective in preventing transmission of HIV to uninfected sexual partners in serodiscordant couples.

Impact

This study has led to international and national guidelines adopting a recommendation for the use of ART for the prevention of transmission in serodiscordant couples. In addition, the WHO cites HPTN 052 as part of the rationale for increasing the CD4 threshold for starting ART to 500 cells/microlitre in 2013. The BHIVA issued a position statement in 2013, stating that, under given conditions, successful ART (undetectable plasma viral load (VL)) is as effective as consistent condom use in limiting viral transmission.

Aims

ART is known to reduce HIV VL in blood and in genital secretions. Transmission of HIV to sexual partners is strongly associated with VL, and this study was designed to evaluate the use of early ART, at higher CD4 counts than recommended for treatment at the time, for the prevention of transmission of HIV in serodiscordant couples (one partner HIV-positive and one HIV-negative).

Methods

Patients: 1,763 couples (at 13 sites in Africa, Asia, and America).

Inclusion criteria:

- Serodiscordant couples in a stable relationship for 3mo;
- Reporting ≥ 3 episodes of vaginal or anal intercourse in 3mo;
- HIV-positive partner willing to disclose to HIV-negative partner;
- HIV-positive partner with CD4 count 350–550 cells/microlitre;
- HIV-positive partner ART-naïve.

Groups: 1:1 to early vs delayed ART, with block randomization stratified by site:

- Early ART ($n = 886$ couples): HIV-positive partner initiated ART at enrolment;
- Delayed ART ($n = 877$ couples): HIV-positive partner initiated ART if CD4 count fell to ≤ 250 cells/microlitre or AIDS-defining condition developed.

Follow-up: Monthly for 3mo, then 3-monthly. All couples received counseling on risk reduction and condom use, and treatment for sexually transmitted infections. HIV-negative partners tested for HIV every 3mo.

Primary endpoint: Linked transmission to the HIV-negative partner (defined by comparison of virus from each partner for genetic similarity of given HIV-1 gene sequences, compared with a sample of sequences from local population).

Secondary endpoints: Not discussed here.

Results

Demographics/baseline:

- 97% couples were heterosexual; 50% of HIV-positive partners ♂;
- Median baseline CD4 counts of HIV-positive partners = 442 and 428 cells/microlitre in early and delayed ART groups, respectively;
- Similar proportions (4%, 6%) reported unprotected sex in the week preceding baseline. Study stopped, after interim analysis showing effect.

Primary outcome:

- 28 linked transmission events: 1 (0.1/100 person-years, 95% CI 0.0–0.4) in early and 27 (1.7/100 person-years, 95% CI 1.1–2.5) in delayed treatment groups;
- HR 0.04 (95% CI 0.01–0.27, $p < 0.001$) for transmission in early vs delayed ART group, after median 1.7y F/U;
- The single linked transmission in early ART group occurred within first 3mo of ART.

Discussion

This trial showed a 96% reduction in transmission rate with early ART and one linked transmission in the early ART group likely to have occurred before full virological suppression. Results support the implementation of policy to use ART as a prevention strategy on an individual or population level.

Problems

- 97% of couples were heterosexual, which limits the extent to which results can be extrapolated to men who have sex with men.
- Relatively short F/U: effect needs verifying over longer period on ART.
- Stable, discordant couples may not represent the general population, and, in many settings, F/U is less intensive than in this study. However, randomization and virological linking of transmission events mean results strongly support the hypothesis of ART being effective at reducing transmission.

Further reading

Donnell D, Baeten J, Kiarie J *et al.* (2010). Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 375, 2092–8.

Continuous vs intermittent antiretroviral therapy

SMART (Strategies for Management of AntiRetroviral Therapy study: CD4+ count-guided interruption of antiretroviral therapy.

AUTHORS: El-Sadr W, Lundgren J, Neaton J et al.

REFERENCE: *N Engl J Med* (2006) 355, 2283–96.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

CD4+ count-guided interruption of ART is inferior to continuous ART, with significantly higher rates of death, opportunistic disease, and renal, hepatic, and CV events.

Impact

Previously, patients and physicians considered interrupting therapy for those with higher CD4+ counts, in the interest of reduced cost and SEs. All now recommend continuous therapy, with greater focus on the CD4 threshold when continuous ART should be initiated.

Aims

Long-term ART is associated with SEs, financial cost, and risk of developing resistance to component drugs. Several studies had investigated possible intermittent treatment strategies to reduce these risks and costs. There were smaller trials published before SMART, demonstrating 'safe' interruption of ART, even in individuals with previous AIDS-defining conditions. This study was powered to conclusively compare two treatment strategies: continuous treatment ('virological suppression' arm) and interrupted treatment ('drug conservation' arm).

Methods

Patients: 5,472 patients from multiple international centres.

Inclusion criteria: HIV-positive with CD4 count >350 cells/microlitre, plus:

- Age >13y, and not pregnant or breastfeeding;
- Consenting to start, stop, or change ART, according to study protocol.

Groups:

- Viral suppression, VS ($n = 2,752$): Received uninterrupted ART, aiming for continuous virological suppression;
- Drug conservation, DC ($n = 2,720$): Received ART if CD4 <250, and discontinued ART if CD4 >350 cells/microlitre.

Primary endpoint: New/recurrent opportunistic disease or death from any cause.

Secondary endpoints:

- Serious opportunistic disease;
- Major CV, hepatic, or renal disease;

- Grade 4 toxicity—potentially life-threatening events requiring medical treatment (as per toxicity tables of the National Institute of Allergy and Infectious Diseases).

Follow-up: At 1 and 2mo, then every 2mo in first year, and every 4mo each following year, with history, examination, ECG, HIV VL, and CD4 count. Patients also assessed if clinical need arose.

Results

- Mean F/U 16mo, before protocol modified for the DC group. ART taken for 33% and 94% of the time in DC and VS groups, respectively. (See Table 12.1.)

Table 12.1 Summary of results

| Primary endpoints | Event rate per 100 person-years | | |
|---|---------------------------------|-----|---------------------------------|
| | DC | VS | HR (95% CI), <i>p</i> |
| Opportunistic disease or death from any cause | 3.3 | 1.3 | 2.6 (1.9–3.7), <i>p</i> < 0.001 |
| Death from any cause | 1.5 | 0.8 | 1.8 (1.2–2.9), <i>p</i> = 0.007 |
| Secondary endpoints | | | |
| Major CV, renal, or hepatic disease | 1.8 | 1.1 | 1.7 (1.1–2.5), <i>p</i> = 0.009 |
| Grade 4 event or death from any cause | 5.9 | 4.7 | 1.3 (1.0–1.6), <i>p</i> = 0.03 |

Discussion

There were relatively few deaths due to opportunistic infections, and, unexpectedly, the DC group did not have fewer grade 4 events than the VS group. The higher rate of CV disease in the DC group challenged the belief that CV toxicity in HIV is entirely related to medication and raised questions about the pro-inflammatory effects of untreated HIV infection. The study was stopped early, with an average of 16mo F/U, rather than the planned 6y, due to the high rate of disease progression and death in the DC group.

Problems

- Early interruption of recruitment and F/U, so data are not long-term.
- No data from SMART on the development of drug resistance with each treatment strategy; this was examined in previous small studies.
- The CD4 count thresholds at which treatment was commenced (<250 cells/microlitre) and interrupted (CD4 >350 cells/microlitre) in the drug conservation arm were low, compared with current recommendations. However, with knowledge accrued from other data sets of the harmful effects of HIV-induced inflammation, SMART proves the harmful effects of this strategy.

Further reading

- Martinez E, Visnegarwala F, Grund B et al. (2010). The effect of intermittent, CD4-guided antiretroviral therapy on body composition and metabolic parameters. *AIDS* 28, 353–63.
- Silverberg J, Neuhaus J, Bower M et al. (2007). Risk of cancers during interrupted antiretroviral therapy in the SMART study. *AIDS* 21, 1957–63.

New antiretroviral agents for treatment-experienced individuals

Efficacy of new antiretroviral drugs in treatment-experienced HIV-infected patients: a systematic review and meta-analysis of recent randomized controlled trials.

AUTHORS: Pichenot M, Deuffic-Burban S, Cuzin L *et al.*

REFERENCE: *HIV Med* (2012) 13, 148–55.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

The number of fully active antiretroviral agents in a combination is the main predictive factor for treatment efficacy in ART-experienced individuals.

Impact

New antiretrovirals, specifically those with a novel mechanism, mean that virological suppression is now an achievable goal in all patients. BHIVA guidelines recommend the use of at least two (preferably three) fully active agents, including one with a novel mechanism, aiming for full virological suppression in all experienced individuals.

Aims

HIV drug resistance is associated with poor outcomes, including virological and immunological failure, clinical progression, and death. This meta-analysis, comparing new drugs with placebo when added to optimized background therapy (OBT), aimed to establish factors associated with treatment efficacy.

Methods

Studies included: Ten studies of new agents—maraviroc and vicriviroc (C–C chemokine receptor type 5 [CCR5] inhibitors); enfuvirtide (fusion inhibitor); raltegravir (integrase inhibitor); etravirine (non-nucleoside reverse transcriptase inhibitor, NNRTI); tipranavir and darunavir (protease inhibitors, PIs).

Inclusion criteria:

- Published between January 2003 and March 2010;
- Enrolled ART-experienced individuals with HIV RNA $\geq 1,000$ copies/mL;
- Outcome at wk 48 of virological and immunological response in groups on new drug vs placebo, both with OBT.

Data included:

- All patients had taken at least one nucleoside reverse transcriptase inhibitor (NRTI), one NNRTI, and one PI for ≥ 3 mo, or had documented resistance to at least two classes;

- Data used were from ITT analyses. Proportions with virological suppression (undetectable HIV RNA) at 48wk were compared, using ORs and 95% CIs (calculated by a random effects model); CD4 increases at wk 48 were analysed using mean differences.

Results

- Ten studies, including a total of 6,401 individuals (one study of maraviroc excluded from analysis of virological efficacy). (See Table 12.2.)

Table 12.2 Summary of results

| Outcome at 48wk | Treatment group | Placebo group | OR (95% CI) | Test for heterogeneity |
|-------------------------|---------------------|--------------------|------------------|------------------------|
| Virological suppression | 41.7% (range 18–64) | 23.6% (range 0–62) | 2.97 (2.11–4.17) | 45%; $p < 0.001$ |

- Greatest effect sizes for virological suppression and immunological recovery seen when trials enrolled mostly men ($p = 0.02$; possibly confounded by greater ART experience and lower genotypic sensitivity score (GSS) in men who have sex with men) and when GSS (a measure of the number of active drugs in the OBT regimen using genotypic resistance testing) was low ($0; \leq 1; \leq 2; p = 0.001$ for each);
- Mean CD4 increase 9–62 cells/microlitre greater in treatment vs placebo groups, with greater increase if lower proportion of the placebo group achieved virological suppression at 48wk. Use of CCR5 inhibitors not associated with greater CD4 improvement than other new agents.

Discussion

In ART-experienced individuals, inclusion of a new agent improved virological suppression, with greater effect if the OBT contained fewer effective drugs. However, adding one drug to a regimen with no effect should be avoided, as resistance to the new agent may easily develop. The most important predictive factor in achieving virological suppression is the number of fully active drugs included in the regimen.

Problems

- Significant heterogeneity of effect size between studies limits interpretation.
- Including trials with F/U >48wk may have revealed resistance and virological rebound among those with regimens of low GSS.
- The meta-analysis set out to examine the overall efficacy of the 'new agents' and the factors associated with increased efficacy. Two key messages that are not evident because of the drug studies involved are:
 - Inclusion of a boosted PI in the regimen is a recognized key factor in durable virological suppression in heavily experienced patients;
 - Success of a regimen is determined by achieving an overall GSS of 3. Hence, the greatest success in this meta-analysis was achieved when the most improvement could be made (i.e. when the GSS was low).

Ritonavir-boosted atazanavir vs efavirenz and comparison of two NRTI backbones

ACTG (AIDS Clinical Trials Group) A5202: Atazanavir plus ritonavir or efavirenz as part of a 3-drug regimen for initial treatment of HIV-1.

AUTHORS: Daar E, Tierney C, Fischl M et al.

REFERENCE: *Ann Intern Med* (2011) 154, 445–56.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Efavirenz and atazanavir/ritonavir have similar efficacy, as part of a three-drug, once-daily regimen with a backbone of abacavir/lamivudine or tenofovir/emtricitabine. Increased rates of virological failure were observed with abacavir/lamivudine, irrespective of the third agent, in patients with baseline VLs of >100,000 copies/mL.

Impact

This study compared two NRTI backbones and two options for the third drug in combination ART for ART-naïve individuals. The trial outcome has led to both efavirenz and atazanavir/ritonavir being recommended as first-line agents in naïve patients, and for abacavir/lamivudine to be restricted to those with baseline VLs of <100,000 copies/mL.

Aims

Treatment guidelines for initial HIV-1 therapy recommend two NRTIs with an NNRTI, a ritonavir-boosted PI, or an integrase inhibitor. This study aimed to establish the comparative efficacy of efavirenz (NNRTI) vs atazanavir/ritonavir (PI), and abacavir/lamivudine (NRTI) vs tenofovir/emtricitabine (NRTI), in ART-naïve HIV-positive individuals and in predefined subgroups.

Methods

Patients: 1,857 patients in the USA and Puerto Rico.

Inclusion criteria:

- HIV-positive with no prior ART;
- No known major resistance mutations (but resistance testing not done in all).

Groups: Randomized 1:1:1:1, with stratification by baseline VL (above or below 100,000 copies/mL), to 1–4 regimens:

- Tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) ($n = 464$);
- Tenofovir/emtricitabine/atazanavir/ritonavir (TDF/FTC/ATZ/r) ($n = 465$);
- Abacavir/lamivudine/efavirenz (ABC/3TC/EFV) ($n = 465$);
- Abacavir/lamivudine/atazanavir/ritonavir (ABC/3TC/ATZ/r) ($n = 463$);
- EFV vs ATZ/r = open-label; TDF/FTC vs ABC/3TC = placebo-controlled.

Follow-up: Assessments at baseline, then 4, 8, 26, 24, and every 12wk to the study end (median F/U 138wk). If enrolled with hepatitis B co-infection and allocated ABC/3TC, transferred to TDF/FTC due to guideline change.

Primary endpoint: Time from randomization to virological failure (confirmed HIV VL $\geq 1,000$ copies/mL between 16 and 24wk or ≥ 200 copies/mL after 24wk). Non-inferiority study with ITT analysis.

Secondary endpoints:

- Safety: time to first grade 3 or 4 adverse event;
- Tolerability: time to change in assigned ART regimen;
- Resistance: to component drugs at virological failure.

Results

Table 12.3 Summary of results

| Regimen | HR (95% CI) | |
|-------------------------------|------------------|------------------|
| | Low VL stratum | High VL stratum |
| ATZ/r vs EFV with ABC/3TC | 1.13 (0.82–1.56) | |
| ATZ/r vs EFV with TDF/FTC | 1.01 (0.70–1.46) | |
| ABC/3TC vs TDF/FTC with EFV | 1.23 (0.77–1.96) | 2.46 (1.20–5.05) |
| ABC/3TC vs TDF/FTC with ATZ/r | 1.25 (0.76–2.05) | 2.22 (1.19–4.14) |

- Time to regimen change longer with ATZ/r than EFV (HR 0.69, 95% CI 0.55–0.86);
- Emergent resistance mutations less frequent with ATZ/r than EFV, with either NRTI ($p < 0.001$). Lower frequency of NRTI mutations at failure on ATZ/r than EFV (with ABC/3TC, $p < 0.001$; with TDF/FTC, $p = 0.046$);
- NRTI allocation unblinded early, due to higher virological failure rates with ABC/3TC than TDF/FTC in higher VL stratum. (See Table 12.3.)

Discussion

ATZ/r and EFV shown to be of equivalent efficacy, regardless of baseline VL; TDF/FTC and ABC/3TC equivalent in the group with baseline VL of $< 100,000$ copies/mL, but higher rate of virological failure in the ABC/3TC arm among those with baseline VL of $> 100,000$ copies/mL.

Problems

Limitations to interpretation—specifically the differences found between the NRTIs at viral loads of $> 100,000$ copies/mL which could have led to bias:

- Neither HLA-B*5701 nor resistance testing were standard of care at enrolment;
- Atazanavir, ritonavir, and efavirenz were open-label;
- The NRTIs were prematurely unblinded in the high VL stratum;
- Thirty-two percent of patients modified or discontinued treatment with their third drug.

Further reading

Sax P, Tierney C, Collier A et al. (2011) Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. *J Inf Dis* 204, 1191–201.

Combination treatment for hepatitis C in HIV-positive individuals

Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of hepatitis C virus genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial.

AUTHORS: Sulkowski M, Pol S, Mallolas J et al.

REFERENCE: *Lancet Infect Dis* (2013) 13, 597–605.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A directly acting antiviral (DAA) against hepatitis C increases SVR rates in non-cirrhotic HIV patients chronically co-infected with genotype 1 HCV.

Impact

Addition of DAA increases SVR, as it does in HCV mono-infection. Triple therapy for HCV 1 is now standard, and regimens with increased potency, tolerability, and convenience, including IFN-free regimens, are in development (many phase 3).

Aims

SVR rates of 14–38% have been reported among HIV-positive individuals with hepatitis C genotype 1 treated with pegylated IFN and ribavirin (PEG-IFN/RBV). This study aimed to evaluate the HCV PI boceprevir, in combination with PEG-IFN and weight-based ribavirin, in individuals with chronic HCV and HIV infections in a phase 2 trial.

Methods

Patients: 99 patients across 30 sites in Europe, and North and South America, of whom 98 started treatment.

Inclusion criteria:

- Age 18–65y and HIV-positive for >6mo;
- Stable with undetectable HIV VL and CD4 >200 cells/microlitre;
- Untreated, chronic HCV, genotype 1, HCV RNA >10,000IU/L, liver biopsy consistent with chronic hepatitis C and no other pathology, without hepatic decompensation; hepatitis B surface antigen negative.

Groups: By Metavir liver fibrosis score and baseline HCV RNA 1:2 to:

- Boceprevir ($n = 64$): (800mg three times daily, tds) for 44wk;
- Control ($n = 34$): PEG-IFN 1.5 micrograms/kg/wk with weight-based ribavirin (600–1,400mg/d) for 4wk, followed by PEG-IFN/RBV plus either placebo.

Follow-up: HCV RNA and safety bloods at F/U. Failure $\leq 2 \log_{10}$ decrease in HCV RNA from baseline at wk 12 (wk 8 of boceprevir) or HCV RNA ≥ 25 IU/L at wk 24 (wk 20 of boceprevir). Control group with treatment

failure at wk 24 had option of receiving triple therapy for 44wk in a cross-over arm. Breakthrough = HCV RNA >1,000IU/L after previous undetectable HCV RNA on treatment.

Primary endpoint: Proportion achieving SVR24 (undetectable HCV RNA at 24wk after the end of therapy).

Secondary endpoints: Safety variables; proportion achieving SVR24 (undetectable HCV RNA at 24wk after the end of therapy).

Results

Table 12.4 Summary of results

| | Control (n = 34) | Boceprevir (n = 64) | p |
|--------------------------------------|------------------|---------------------|--------|
| Baseline characteristics | | | |
| ♂ | 22 (65%) | 46 (72%) | — |
| HCV RNA >800,000IU/L | 30 (88%) | 56 (88%) | — |
| Cirrhosis | 1 (3%) | 2 (3%) | — |
| IL28B CC genotype* | 6/29 (21%) | 16/54 (30%) | — |
| Outcomes | | | |
| Proportion with SVR24 | 10 (29%) | 40 (63%) | 0.0008 |
| Virological breakthrough | 0 | 4 (6%) | — |
| Drug discontinuation (adverse event) | 3 (9%) | 13 (20%) | — |
| Anaemia (Hb <100g/L) | 9 (26%) | 26 (41%) | — |

* Numbers given of those known, some IL28B results missing or inconclusive. Host IL28B genotype CC associated with improved HCV clearance rates, compared with non-CC.

- Four entered the cross-over group, of whom three achieved SVR24. (See Table 12.4.).

Discussion

Boceprevir with PEG-IFN/RBV significantly improved numbers achieving SVR24 vs PEG-IFN/RBV. The safety profile is similar to that in HCV mono-infection. With the use of effective ART for HIV, liver disease is an increasingly important cause of death among HIV-positive individuals, and effective treatments are needed for chronic HCV.

Problems

- Strict inclusion. Larger studies needed to confirm efficacy and safety.
- Subsequent pharmacokinetics studies on antiretrovirals used in the study have shown significant interactions, with falls in antiretrovirals to less than half when used with boceprevir—several patients lost HIV virological control.
- Increased frequency/severity of adverse events than HCV mono-infection.

Further reading

Sulkowski M, Sherman K, Dieterich D *et al.* (2013). Combination therapy with telaprevir for chronic hepatitis C virus genotype 1 infection in patients with HIV: a randomised trial. *Ann Int Med* 159, 86–96.

Early antiretroviral therapy in HIV-associated tuberculosis

STRIDE study (Aids Clinical Trials Group, ACTG A5221): Timing of antiretroviral therapy for HIV-1 infection and tuberculosis.

AUTHORS: Havlir D, Kendall M, Ive P *et al.*

REFERENCE: *N Engl J Med* (2011) 365, 1482–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

ART initiated within 2wk of TB treatment in individuals with HIV-associated TB and CD4 counts of <50 cells/microlitre reduces the incidence of AIDS-defining illnesses and death, compared with later ART initiation between 8 and 12wk. An increased rate of immune reconstitution inflammatory syndrome (IRIS) occurred in the early treatment group but responded to conservative management, with no deaths.

Impact

Guidelines have changed internationally, following this and two similar trials, to recommend much earlier initiation of ART, within 2wk of starting TB treatment for those with low CD4 counts, and to manage IRIS if it occurs.

Aims

HIV-associated TB is associated with low CD4 counts and high mortality. The treatment of individuals with both infections is complicated by high pill burden, drug–drug interactions, drug toxicity, and IRIS. This trial aimed to establish the optimal timing of ART initiation in real clinical settings.

Methods

Patients: 806 individuals at 26 sites in North and South America, Africa, and Asia.

Inclusion criteria: HIV-positive with CD4 count of <250 cells/microlitre and:

- Age ≥ 13 y;
- ART-naïve;
- Confirmed (smear- or culture-positive) or probable (treated empirically) TB; pulmonary or extra-pulmonary, without suspected drug-resistance.

Groups: Open-label randomization, stratified by CD4 count (< or ≥ 50 cells/microlitre) and balanced according to site:

- Early ART ($n = 405$): ART initiated within 2wk of TB treatment;
- Later ART ($n = 401$): ART initiated between 8 and 12wk after TB treatment.

Follow-up: Clinical and laboratory evaluation at 4, 8, 12, 16, then every 8wk up to 48wk.

Primary endpoint: Proportion surviving to wk 48 without a new AIDS-defining illness.

Secondary endpoint: TB IRIS (defined by established clinical criteria).

Results

- A total of 806 individuals enrolled (of 809 screened), with median baseline CD4 count of 77 cells/microlitre; 46% had microbiologically confirmed TB. (See Table 12.5.)

Table 12.5 Summary of results

| Outcome | Early ART group | Later ART group | Hypothesis test results |
|---|-----------------|-----------------|--------------------------------|
| Death or AIDS-defining illness (any CD4 count) | 52/405 (13%) | 64/401 (16%) | 95% CI -1.8 to 8.1; $p = 0.45$ |
| Death or AIDS-defining illness (CD4 <50 cells/microlitre) | 23/144 (16%) | 38/141 (27%) | 95% CI 1.5–20.5; $p = 0.02$ |
| TB IRIS* | 43/405 (11%) | 19/401 (5%) | $p = 0.002$ |

* No deaths attributed to IRIS.

Discussion

In individuals with the lowest CD4 counts, early ART improves mortality and disease progression (47% decrease). IRIS occurred more frequently in the early ART group but was not fatal and could be managed. Early ART is therefore safe in HIV-associated TB and must be given for those at risk of disease progression. Results are consistent with those from two other studies conducted around the same time.

Problems

- Not all TB was microbiologically confirmed, although this reflects real practice in many settings.
- The study excluded those with drug-resistant TB.
- Efavirenz dose not weight-adjusted.

Further reading

Abdool Karim S, Naidoo K, Grobler A, et al. (2010). Timing of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* **362**, 697–706 (SAPIT study).

Blanc F, Sok T, Laureillard D et al.; CAMELIA Study Team (2011). Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med* **365**, 1471–81.

Infectious diseases and tropical medicine

Introduction 330

Tuberculous meningitis: steroids 332

Severe falciparum malaria: artesunate vs quinine (1) 334

Severe falciparum malaria: artesunate vs quinine (2) 336

Enteric fever: antibiotic therapy 338

Brucellosis: antibiotic therapy 340

Lyme disease: antibiotic therapy 342

Hepatitis C: predictors of response 344

Introduction

Some of the earliest clinical trials were conducted in infectious diseases. In the 1940s, the development of the first antibiotics for treating TB coincided with the recognition that rigorous clinical trials were required to determine optimum drug combinations and the duration of treatment. Key early trials funded by the MRC included a study comparing streptomycin with the then standard treatment for pulmonary TB—bed rest.¹ The joint efforts of bacteriologists, clinicians, and statisticians promoted the development of clinical trials, acknowledging that clinically valid endpoints and careful statistical analysis are vital for trials to provide evidence of sufficient quality to guide clinical practice.

Infectious diseases was then dominated by antibiotic trials, often funded by drug companies with their own agendas. However, the last decade has seen the publication of a range of important trials, many conducted in resource-poor settings and addressing important clinical questions.

For this chapter, we chose key questions in our field that had been addressed by good-quality trials. We wanted our chapter to be useful for both clinicians in the UK and overseas. We then used a democratic process to evaluate the evidence whereby key papers were allocated to clinicians at the Hospital for Tropical Diseases in London, and our Evidence-Based Medicine sessions were used to evaluate the trials, following a structure very similar to that used in the *Oxford Handbook of Key Clinical Evidence*.² All the medical staff contributed to these sessions which generated intense discussions, resulting in the rejection of a number of trials judged to be of inferior quality, not representative, or not relevant. It was sometimes difficult to select a single trial in any one area, since clinical practice often evolves, based on the collated evidence of multiple trials, each with their own strengths and weaknesses.

We chose trials that generated key data such as the study in Vietnam which examined the effect of adding corticosteroids to the treatment regime for tuberculous meningitis; based on this study, adjunct steroids have now become part of routine practice. Another key trial is the comparison of quinine vs artesunate for the treatment of falciparum malaria which shows that, in Asia, and then in Africa (AQUAMAT, Dondorp *et al.* *Lancet* (2010) 376, 1647–57), treatment with artesunate results in reduced mortality. Other trials address clinical problems that are important worldwide and less commonly seen in the UK, such as the management of cerebral TB, where critical evaluation of current trials might be difficult.

Despite the early studies on TB, this disease is again becoming a major clinical problem worldwide. Among other appropriately designed trials, we hope that, in future editions, we shall be reporting trials looking at novel anti-tuberculous drugs.

References

1. [No authors listed] (1948). Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 2, 769–82.
2. Lockwood DNJ, Armstrong M, Grant A (2004). Integrating evidence based medicine into routine clinical practice: seven years' experience at the Hospital for Tropical Diseases, London. *BMJ* 329, 1020–3.

Tuberculous meningitis: steroids

Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults.

AUTHORS: Thwaites G, Bang N, Dung N et al.

REFERENCE: *N Engl J Med* (2004) 351, 1741–51.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In tuberculous meningitis (TBM), 6–8wk of dexamethasone, administered with initial anti-tuberculous chemotherapy, reduces overall mortality, compared with placebo. In patients presenting with mild (grade I) disease, dexamethasone also reduces the combined risk of death or severe disability.

Impact

Corticosteroids are considered safe in the management of tuberculous meningitis and are routinely administered as part of its management.

Aims

TBM is one of the most severe forms of *Mycobacterium tuberculosis* infection. Small studies had suggested a reduction in severity, and subsequently improved outcomes, following steroid use to diminish the inflammatory response. This trial was designed to examine the effect of dexamethasone on mortality and neurological outcome in the treatment of TBM in adolescents and adults.

Methods

Patients: 545 patients at two centres in Ho Chi Minh City, Vietnam.

Inclusion criteria:

- Age >14y;
- Meningism and cerebrospinal (CSF) abnormalities;
- Acid-fast bacilli seen in CSF ('definite' TBM); or seen in any other specimen/evidence of active pulmonary/extra-pulmonary TB ('probable' TBM); or ≥4 of TB history, CSF lymphocytosis, CSF:plasma glucose <0.5, yellow CSF, altered consciousness, focal neurology, illness duration >5d ('possible' TBM).

Groups: All received streptomycin IM (3mo), and PO rifampicin, isoniazid, and pyrazinamide (6mo). Ethambutol replaced streptomycin if HIV-infected; added for 3mo, if previous TB treatment.

- Dexamethasone ($n = 274$; including 44 with HIV infection);
- Placebo ($n = 271$; including 54 with HIV infection).

Dosage: Dexamethasone group with grade I disease (GCS 15, no focal neurology) received 2wk of dexamethasone IV (0.3mg/kg/d wk 1; 0.2mg/kg/d wk 2); then 4wk of oral therapy (0.1mg/kg/d wk 3; 3mg/kg/d wk 4;

reduced by 1mg each wk). Grades II (GCS 11–14) and III (GCS ≤ 10) disease received 4wk of dexamethasone IV (0.4mg/kg/d wk 1; reduced by 0.1mg/kg/d each wk); then 4wk of oral therapy (4mg total/d; decreased by 1mg each wk).

Primary endpoint: Death or severe disability at 9mo.

Secondary endpoints:

- Fever and coma clearance time, time to discharge from hospital;
- Time to relapse (new focal neurology or decreased GCS);
- Adverse events, including hepatitis, GI bleeding, bacterial sepsis.

Follow-up: At 1, 2, 6, and 9mo. The latest assessment time point was carried forward in ten patients lost to F/U at 9mo.

Results

Table 13.1 Summary of results

| Primary endpoints | Dexamethasone | Placebo | p |
|---|---------------|---------------|-------|
| Death (all patients) | 87 (31.8%) | 112 (41.3%) | 0.01 |
| Death/severe disability (grade I disease) | 19/90 (21.1%) | 30/86 (34.9%) | 0.04 |
| Secondary endpoints | | | |
| Fever clearance | Median 9d | Median 11d | 0.03 |
| Severe adverse events | 26 (9.5%) | 45 (16.6%) | 0.02 |
| Severe clinical hepatitis | 0 (0.0%) | 8 (3.0%) | 0.004 |

Discussion

Although overall mortality was reduced, there was no reduction in the combined outcome of death or severe disability in the dexamethasone group. This may, in part, be due to the greater proportion of survivors in the dexamethasone group who presented with moderate or severe (grade II or III) disease. In patients with mild (grade I) disease, there was a small, but significant, reduction in the combined primary endpoint in the dexamethasone group. There was no significant difference in coma clearance time, time to discharge, or relapse rates between the groups, but there were significantly fewer adverse events with dexamethasone. (See Table 13.1.)

Problems

- Dexamethasone regimes differed in patients with grade I vs II/III disease, and, although anti-tuberculous drugs were administered via a nasogastric tube in those unable to swallow, dexamethasone was always administered IV for the first 2 or 4wk. As bioavailability of oral steroids is usually good, some advocate equivalent-dose oral protocols, rather than the dexamethasone regimes used here.
- Twenty percent had coexistent HIV (median CD4 count 66/mm³). None received ART. Overall mortality in these patients was higher (65%) than in HIV-negative subjects (28%) at a steady rate throughout F/U. Study not sufficiently powered to assess the impact of corticosteroids in this population, although most would recommend their use.

Severe falciparum malaria: artesunate vs quinine (1)

SEAQUAMAT (South East Asian Quinine Artesunate Malaria Trial): Artesunate vs quinine for treatment of severe falciparum malaria.

AUTHORS: SEAQUAMAT group.

REFERENCE: *Lancet* (2005) **366**, 717–25.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In the treatment of severe falciparum malaria, artesunate reduces mortality by around one-third vs standard treatment with quinine. Artesunate also results in a reduced incidence of hypoglycaemia and is easier to administer than quinine.

Impact

Where quality-assured supply is available, artesunate should replace quinine as the treatment of choice for severe falciparum malaria.

Aims

The artemisinin derivatives artemether and artesunate rapidly kill *Plasmodium falciparum* parasites and, in contrast to quinine, kill both circulating ring-form trophozoites and cytoadhering schizont stages. Unlike artemether, artesunate is water-soluble and can be administered IV. This trial was designed to establish whether artesunate IV could reduce mortality in the treatment of severe malaria, compared with established therapy using quinine IV.

Methods

Patients: 1,461 patients (577 Myanmar, 453 Bangladesh, 289 Indonesia, 142 India).

Inclusion criteria: Clinical diagnosis of severe malaria, and:

- Age >2y;
- Positive blood antigen stick test for *P. falciparum* (95% of subjects were peripheral blood film-positive);
- Patients were excluded if treated with either quinine or artemisinin derivative for >24h prior to admission.

Groups: Both groups received doxycycline (100mg bd PO for 7d) if PO medication was tolerated (unless <8y or pregnant), and full supportive measures according to WHO guidelines:

- Artesunate (2.4mg/kg IV as a bolus at 0, 12, and 24h, then daily); switched to PO when tolerated (2mg salt/kg/d); to complete a total course of 7d ($n = 730$; 633 adults, 97 children (<15y); 509 (70%) with severe malaria);

- Quinine dihydrochloride (20mg/kg IV loading dose over 4h); then 10mg/kg over 2–8h (tds); switched to PO (10mg/kg tds) when tolerated, to complete a total course of 7d ($n = 731$; 626 adults, 105 children (<15y); 541 (74%) with severe malaria).

Primary endpoint: Death from severe malaria (in-hospital mortality). Severe malaria: defined as a positive blood film and any one of the following: GCS <11/15 (adults), Blantyre coma scale <3 (children), shock, respiratory rate >32/min, plasma glucose <2.2mmol/L, blood bicarbonate <15mmol/L, haematocrit <20%, or jaundice and parasitaemia >100,000/microlitre, blood urea >17mmol/L, parasitaemia >10%.

Secondary endpoints:

- Incidence of neurological sequelae;
- Recovery times (times to eat, speak, sit) and time to hospital discharge;
- Development of severe complications.

Results

Table 13.2 Summary of results

| Primary endpoint | Artesunate | Quinine | <i>p</i> |
|----------------------------|---------------|--------------|----------|
| Death | 107/730 (15%) | 64/731 (22%) | 0.0002 |
| Secondary endpoints | | | |
| Neurological sequelae | 7/730 (1%) | 3/731 (<1%) | 0.2 |
| Hypoglycaemia | 6/730 (<1%) | 19/731 (3%) | 0.009 |

- No significant differences in recovery times and time to discharge. (See Table 13.2.)

Discussion

Overall mortality in this trial was 19% (24% in patients with severe malaria), ranging from 9.3% in Indonesia to 28% in Bangladesh. The superior efficacy of artesunate was consistent across high and low mortality centres. Most of the reduction in mortality attributable to artesunate occurred 24–48h after entry to the study (23 and 29 patients died on the day of admission in artesunate and quinine groups, respectively, $p = 0.4$). Reduction in mortality was particularly marked in patients with parasitaemia >10% (mortality 23% artesunate group vs 53% quinine group), implying *in vivo* confirmation of superior parasitocidal activity of artesunate. Just as PO artemisinin derivatives are beginning to replace quinine as the treatment of choice for uncomplicated falciparum malaria, artesunate is now indicated as the optimum treatment for severe cases.

Problems

- The overall mortality in the 202 children aged <15y was only 8%: 5% in the artesunate group, and 11% in the quinine group ($p = 0.2$). Thus, although the treatment effect of artesunate mirrored that seen in adults, this study was not sufficiently powered to demonstrate an unequivocal benefit of artesunate vs quinine in children.
- Parenteral artesunate manufactured to appropriate standards is not routinely available in many parts of the world, compromising implementation of this trial's 1^o recommendation.

Severe falciparum malaria: artesunate vs quinine (2)

AQUAMAT: Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial.

AUTHORS: SEAQUAMAT group.

REFERENCE: *Lancet* (2005) **366**, 717–25.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In the treatment of severe falciparum malaria in African children, artesunate reduces mortality by around one-third vs standard treatment with quinine. Artesunate also results in reduced incidence of hypoglycaemia and is easier to administer than quinine.

Impact

Where quality-assured supply is available, artesunate should replace quinine as the treatment of choice for severe falciparum malaria.

Aims

Following on from the success of SEAQUAMAT, this trial was designed to establish whether artesunate IV could reduce mortality in the treatment of severe malaria, compared with established therapy using quinine IV, in the population most at risk—African children.

Methods

Patients: 5,425 patients (from 11 centres in nine countries—Mozambique, The Gambia, Ghana, Kenya, Tanzania, Nigeria, Uganda, Rwanda, and Democratic Republic of the Congo).

Inclusion criteria: Clinical diagnosis of severe malaria, and:

- Age >2y;
- Positive blood antigen stick test for *P. falciparum* (95% of subjects were peripheral blood film-positive);
- ≥1 of: plasma base excess < -3.3mmol/L; GCS <11 of 15 or Blantyre coma scale <3 of 5 in preverbal children; Hb <50g/L and parasitaemia >100,000 parasites/microlitre; blood urea >10mmol/L; compensated shock (capillary refill ≥3s or temperature gradient on legs, but no hypotension); decompensated shock; SBP <70mmHg and cool peripheries; asexual parasitaemia >10%; visible jaundice and >100,000 parasites/microlitre; plasma glucose <3mmol/L; respiratory distress (defined as costal indrawing, use of accessory muscles, nasal alar flaring, deep breathing, or severe tachypnoea).

Exclusion criteria: Treated with either quinine or artemisinin derivative for >24h prior to admission.

Groups:

- Artesunate (2.4mg/kg IV as a bolus at 0, 12, and 24h, then daily); switched to PO Coartem™ ($n = 2,712$; 149 excluded from protocol analysis);
- Quinine dihydrochloride (20mg/kg IV loading dose over 4h); then 10mg/kg over 2–8h (tds); switched to PO Coartem™ when tolerated ($n = 2,713$);
- When the patient was able to take tablets, but after a minimum of 24h of parenteral treatment, PO artemether–lumefantrine (Coartem™, Novartis, Basel, Switzerland) in a full standard dose (one·5/9 mg/kg bd for 3d with milk or fat) was given to complete the treatment. Full supportive measures, according to WHO guidelines, were given:

Primary endpoint: Death from severe malaria (in-hospital mortality) on an ITT basis.

Secondary endpoints: Incidence of severe neurological complications (at 28d, 3–8wk) and combined outcome measure of death and severe persistent neurological sequelae. Initially, neurological outcomes assessed only at discharge from hospital, but this led to substantial overestimation of neurological deficit, especially in young children. The protocol therefore changed in April 2007 (after 11% enrolled), so children not fully recovered at discharge were assessed 28d after enrolment, and active follow-up instituted.

Results

Table 13.3 Summary of results

| Primary endpoint | Artesunate | Quinine | <i>p</i> |
|----------------------------|------------------|-------------------|----------|
| Death | 230/2,712 (8.5%) | 297/2,713 (10.9%) | 0.0022 |
| Secondary endpoints | | | |
| Neurological sequelae | 24/706 (1%) | 23/737 (<1%) | 0.2 |
| Hypoglycaemia | 48/2,712 (1.8%) | 75/2,713 (2.8%) | 0.0134 |

- No significant differences in recovery times and time to discharge. (See Table 13.3.)

Discussion

Overall mortality in this trial was 9.7%. There was no heterogeneity between sites. The superior efficacy of artesunate was consistent across high and low mortality centres. Before this trial, concerns had been raised that artesunate might not be better than quinine in African children, whereas it clearly was in Asian patients in SEAQUAMAT. The concerns arose, because of perceived differences in pathology and the prevalence of more quinine-susceptible malaria parasites in Africa. In SEAQUAMAT, the survival curves did not separate clearly, until 48h after starting treatment, whereas most deaths in African children occurred before this time. The findings were robust and led to the WHO recommendation of artesunate as first-line therapy.

Problems

- Overall mortality was only 9.7%.
- Artesunate manufactured to appropriate standards was not routinely available in many regions, compromising this trial's 1° recommendation. Artesunate is also more expensive than quinine in Africa.

Enteric fever: antibiotic therapy

Randomized controlled comparison of ofloxacin, azithromycin, and an ofloxacin–azithromycin combination for treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever.

AUTHORS: Parry C, Anh Ho V, Thi Phuong L et al.

REFERENCE: *Antimicrob Agents Chemother* (2007) 51, 819–25.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In multidrug-resistant (MDR) *Salmonella enterica* serovar *Typhi* with reduced fluoroquinolone susceptibility, 1wk of PO azithromycin is superior to ofloxacin and an ofloxacin–azithromycin combination in clearance and faecal carriage post-therapy.

Impact

Azithromycin may be considered in preference to fluoroquinolones in the treatment of uncomplicated typhoid fever acquired in settings where reduced fluoroquinolone susceptibility is common.

Aims

MDR typhoid is an increasing problem, particularly in Asian countries where disease is endemic. This study was designed to compare 7d of PO azithromycin with ofloxacin or combined therapy in the treatment of uncomplicated typhoid fever due to MDR *S. enterica* serovar *Typhi* (resistant to ampicillin, chloramphenicol, and trimethoprim–sulfamethoxazole) and with reduced fluoroquinolone susceptibility (nalidixic acid-resistant).

Methods

Patients: 199 culture-positive patients at one infection ward in Vietnam.

Inclusion criteria: Fever $\geq 38^{\circ}\text{C}$ for $\geq 4\text{d}$ and ≥ 1 of following: abdominal pain, diarrhoea/constipation, hepato- or splenomegaly, rose spots.

Exclusion criteria:

- Severe/complicated disease (intestinal bleeding/perforation, jaundice, myocarditis, pneumonia, renal failure, shock, or altered conscious level);
- Inability to swallow PO medication, drug hypersensitivity, pregnancy;
- Treatment with fluoroquinolone, extended-spectrum cephalosporin, or macrolide within 1wk of admission.

Groups:

- Ofloxacin (20mg/kg/d PO, max 400mg bd, for 7d) ($n = 63$);
- Azithromycin (10mg/kg/d PO, max 500mg od, for 7d) ($n = 62$);
- Ofloxacin (15mg/kg/d PO, max 300mg bd, for 7d) and azithromycin (10mg/kg/d PO, max 500mg od, for the first 3d) ($n = 62$).

Primary endpoints: Clinical treatment failure (fever persistence and ≥ 1 typhoid-related symptom > 7 d after treatment start, or development of severe complication) and microbiological treatment failure (*S. enterica* serovar *Typhi* isolation from blood/other sterile site post-treatment).

Secondary endpoints:

- Faecal carriage immediately after treatment;
- Mean fever clearance time (time from treatment start to temperature $\leq 37.5^{\circ}\text{C}$ and remaining $\leq 37.5^{\circ}\text{C}$ for 48h);
- Relapse rates (recurrence of symptoms/signs and blood cultures positive for *S. enterica* serovar *Typhi*).

Follow-up: At 4wk, 3mo, and 6mo.

Results

- Of 187 eligible patients: 163 (87%) = age < 15 y; 165 (88%) = infected with MDR isolate; 173 (93%) = nalidixic acid-resistant isolate;
- All isolates susceptible to ofloxacin by disc test (majority had minimal inhibitory concentration (MIC) 0.5–1.0 micrograms/mL). (See Table 13.4.)

Table 13.4 Summary of results

| Primary endpoints | Ofloxacin | Ofloxacin and azithromycin | Azithromycin | <i>p</i> |
|----------------------------|------------|----------------------------|--------------|-----------|
| Clinical failure | 23 (36.5%) | 15 (24.2%) | 11 (17.8%) | 0.05 |
| Microbiological failure | 2 (3.2) | 1 (1.6%) | 2 (3.2%) | 0.8 |
| Secondary endpoints | | | | |
| Fever clearance time | 8.2d | 7.1d | 5.8d | < 0.001 |
| Faecal carriage | 12 (19.4%) | 4 (6.5%) | 1 (1.6%) | 0.006 |

Discussion

Clinical failure was commoner with ofloxacin alone than with azithromycin and ofloxacin–azithromycin, and there was a significant difference in fever clearance times. Ofloxacin-treated patients were more likely to be faecal culture-positive immediately post-treatment. There were no other outcome differences between the groups, including the proportion with blood culture positivity after treatment, length of hospital stay, and faecal carriage rates at any time during 6mo F/U. There were no relapses and no treatment-limiting adverse effects of therapy.

Problems

- Despite evidence for first-line azithromycin in areas where nalidixic acid-resistant MDR strains are common, more evidence is required to change practice in settings where the higher cost of azithromycin is an issue and when applying the results to adults (87% of patients < 15 y old).
- Ceftriaxone remains the gold standard for MDR nalidixic acid-resistant typhoid fever. Study unblinded and re-treatment after initial failure was at the physician's discretion; all those re-treated responded to 7–10d of ceftriaxone.

Brucellosis: antibiotic therapy

Doxycycline-rifampin versus doxycycline-streptomycin in treatment of human brucellosis due to *Brucella melitensis*.

AUTHORS: Solera J, Rodriguez-Zapata M, Geijo P et al.

REFERENCE: *Antimicrob Agents Chemother* (1995) **39**, 2061–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Doxycycline–streptomycin is superior to doxycycline–rifampicin in the treatment of acute brucellosis, resulting in fewer early therapeutic failures and relapses 12mo after treatment. Both regimens are well tolerated, with <5% of patients experiencing treatment-limiting adverse effects.

Impact

Doxycycline–streptomycin should be considered for first-line treatment of acute brucellosis.

Aims

Brucellosis, although predominantly a disease of the Mediterranean, the Middle East, and Latin America, can be acquired through contaminated dairy products and occupational exposure in other parts of the world. The optimum antimicrobial regimen for its acute treatment is not clearly established. Tetracycline–streptomycin combinations were considered standard therapy, until the WHO changed its recommendation to a 6wk doxycycline–rifampicin combination in 1986. This trial was designed to compare the efficacy and safety of doxycycline–streptomycin and doxycycline–rifampicin for the treatment of acute brucellosis due to *Brucella melitensis*.

Methods

Patients: 194 patients presenting to five hospitals in Spain.

Inclusion criteria:

- Age >7y;
- *Brucella* species isolated from blood or other fluid or tissue ($n = 120$) or positive *Brucella* serology—agglutination titre for anti-*Brucella* antibodies >1:160 and compatible clinical findings ($n = 74$).

Exclusion criteria: Including:

- Endocarditis or neurobrucellosis;
- Pregnancy, breastfeeding, or allergy to study antimicrobials;
- Antibiotic therapy for brucellosis within 7d of study entry.

Groups:

- Doxycycline (100mg bd PO) plus rifampicin (900mg od PO) for 45d ($n = 100$);
- Doxycycline (100mg bd PO for 45d) plus streptomycin (1g od IM for 14d) ($n = 94$).

Primary endpoint: Absence of relapse (symptoms, signs, or new positive blood cultures 12mo after therapy completion).

Secondary endpoints:

- Early therapeutic failure (symptoms/signs persisting >4wk of therapy);
- Time to defervescence.

Follow-up: Initial assessments at d 0, 7–14, and 45; then at 1, 3, 6, and 12mo, following completion of therapy.

Results

Table 13.5 Summary of results

| Primary endpoint | Doxycycline + rifampicin | Doxycycline + streptomycin | <i>p</i> |
|----------------------------|--------------------------|----------------------------|----------|
| Relapses | 16/100 (16%) | 5/94 (5.3%) | 0.02 |
| Secondary endpoints | | | |
| Early therapeutic failure | 8/100 (8%) | 2/94 (2%) | 0.1 |
| Mean time to defervescence | 4.6d | 4.3d | ns |

Discussion

Earlier trials for the treatment of brucellosis had shown relapse rates of 30–40% with doxycycline plus rifampicin given for <6wk, but rates of only 0–8% with >30d addition of tetracycline plus ≥14d of streptomycin. Furthermore, previous small studies had failed to show significant differences between outcomes with doxycycline plus rifampicin (45d) and doxycycline (45d) plus streptomycin (14–21d). However, this larger trial, which combined relapses with early therapeutic failure, found 24% failed to respond to doxycycline–rifampicin vs only 7% failing to respond to doxycycline–streptomycin ($p = 0.002$). Both regimens were well tolerated, with only four patients in the doxycycline–rifampicin group, and two in the doxycycline–streptomycin group, experiencing treatment-limiting adverse effects. (See Table 13.5.)

Problems

- Clinical endpoints are difficult to define in human brucellosis. Study unblinded, as deemed unethical to include a 14d IM placebo group.
- The superior outcome with doxycycline–streptomycin must be weighed against the inconvenience, increased cost, and potential toxicity of IM streptomycin, compared with PO rifampicin.
- Relapses (in which 13 out of 21 subjects had *Brucella* bacteraemias) could not be distinguished from re-infection with *B. melitensis*. Twenty of these 21 subjects responded to a second alternative course of antibiotics (15 received doxycycline–streptomycin). One patient required a third antibiotic course after a second relapse.

Lyme disease: antibiotic therapy

Duration of antibiotic therapy for early Lyme disease.

AUTHORS: Wormser G, Ramanathan R, Nowakowski J et al.

REFERENCE: *Ann Intern Med* (2003) 138, 697–704.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Clinical response rates do not differ significantly in patients treated for early Lyme disease with either 10 or 20d of doxycycline, and are not enhanced by the addition of a single initial dose of IV ceftriaxone.

Impact

A 10d course of doxycycline is regarded by some as sufficient treatment for early Lyme disease presenting as erythema migrans.

Aims

Erythema migrans is the commonest manifestation of Lyme disease. For uncomplicated presentations, neither the optimum duration of antibiotic therapy nor whether outcomes were improved by routine use of CSF-penetrating antibiotics had been established. This trial aimed to evaluate prolonged vs short course of PO doxycycline for uncomplicated early Lyme disease and to determine whether outcomes were improved by an initial bolus dose of IV ceftriaxone.

Methods

Patients: 180 outpatients at one centre in New York, USA.

Inclusion criteria:

- Age >16y, with diagnosis of uncomplicated early Lyme disease;
- Erythema migrans (annular skin lesion >5cm in diameter).

Exclusion criteria:

- Received >48h of antibiotic therapy for Lyme disease;
- Lyme meningitis or heart block;
- 'Any underlying condition' that might compromise assessment or F/U.

Groups:

- Single dose of ceftriaxone (2g IV); then 10d of doxycycline (100mg bd PO); then 10d of placebo (PO) ($n = 60$; 54 evaluable);
- Placebo (IV); then 10d of doxycycline (100mg bd PO); then 10d of placebo (PO) ($n = 61$; 50 evaluable);
- Placebo (IV); then 20d of doxycycline (100mg bd PO) ($n = 59$; 45 evaluable).

Primary endpoints:

- **Early response at 20d:** *Complete response* (no recurrence of erythema migrans, no other objective manifestations of Lyme disease, return to pre-disease health); *partial response* (no recurrence of erythema migrans, but subjective symptoms); *failure* (any of: no clinical improvement by d10; recurrence of erythema migrans or fever attributable to Lyme disease; objective cardiac, neurological, or rheumatological manifestations of disease not present in first 10d);
- **Late response at 3, 12, and 30mo:** *Complete response* (as above); *partial response* (as above; no objective, but subjective, symptoms of uncertain aetiology); *failure* (objective manifestations of disease).

Secondary endpoints:

- Neurocognitive evaluation scores (baseline, 12mo, and 30mo);
- Drug-induced adverse events.

Follow-up: At 10 and 20d; then at 3, 6, 12, 24, and 30mo; included neurological examination and neurocognitive testing.

Results

Table 13.6 Summary of results

| Primary endpoints | 10d doxycycline and ceftriaxone | 10d doxycycline | 20d doxycycline |
|----------------------------|---------------------------------|-----------------|-----------------|
| Complete response (20d) | 43/52 (65.4%) | 34/48 (70.8%) | 29/45 (64.4%) |
| Complete response (30mo) | 32/37 (86.5%) | 28/31 (90.3%) | 26/31 (83.9%) |
| Partial response (30mo) | 5/37 (13.5%) | 2/31 (6.5%) | 5/31 (31.0%) |
| Secondary endpoints | | | |
| Diarrhoea | 21/60 (35.0%) | 4/61 (6.6%) | 5/59 (8.5%) |

Discussion

No significant differences in complete response, partial response, and failure between the groups at all F/U points. Treatment failure occurred in only one patient (10d doxycycline group) who developed Lyme meningitis at 18d and recovered fully after 2wk of IV ceftriaxone. No significant differences between groups in neurocognitive testing. Significantly more patients in the ceftriaxone–doxycycline group (35%) developed diarrhoea than in the doxycycline alone groups ($p < 0.001$). (See Table 13.6.)

Problems

- Uncertain impact of broad exclusion of ‘any underlying condition’.
- Rates of post-Lyme disease syndrome lower than expected, with >83% demonstrating complete response at 30mo; small number of evaluable patients meant study underpowered to detect small differences.
- 48–65% took additional antibiotics for intercurrent infections.
- In those deemed to have a partial response, there was no evaluation of the subjective symptoms to exclude causes other than Lyme disease.
- *Borrelia burgdorferi* genospecies and clinical manifestations differ between the USA and Europe; conclusions not necessarily applicable to Europe.

Hepatitis C: predictors of response

Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance.

AUTHORS: Ge D, Fellay J, Thompson AJ *et al.*

REFERENCE: *Nature* (2009) **461**, 399–401.

STUDY DESIGN: RCT (genome-wide association study).

EVIDENCE LEVEL: 1b.

Key message

A genetic polymorphism can predict spontaneous clearance and response to treatment in HCV infection.

Impact

IL28B polymorphism determined before commencing treatment with pegylated interferon- α (PEG-IF) and ribavirin (RBV).

Aims

HCV infects 3% of the world population. Chronic HCV treatment consists of combination PEG-IF and RBV for 48wk. Many are not cured, though European patients have significantly higher probability of cure than Africans. Treatment often poorly tolerated due to SEs that prevent some from completing therapy. This genome-wide association study (GWAS) aimed to identify genetic determinants of response to treatment.

Methods

Patients: 1,600 patients who were part of the IDEAL study (RCT of differing doses of PEG-IF plus RBV), and 67 patients from another prospective study.

Inclusion criteria:

- Age ≥ 18 y;
- Compensated liver disease due to chronic HCV genotype 1 infection and a detectable plasma HCV RNA level;
- Not previously treated for hepatitis C infection;
- Absolute neutrophil count $\geq 1,500/\text{mm}^3$, platelet count $\geq 80,000/\text{mm}^3$, and Hb $\geq 12\text{g/dL}$ (women) or $\geq 13\text{g/dL}$ (men).

Exclusion criteria:

- Co-infection with HIV or HBV;
- Any other cause of liver disease;
- Poorly controlled DM ($\text{HbA}_{1c} > 8.5\%$);
- Morbid obesity (weight $> 125\text{kg}$);
- Severe depression/psychiatric disorder, or active substance abuse.

Groups: Randomly assigned in 1:1:1 ratio to a group stratified by HCV RNA level ($\leq 600,000\text{IU/mL}$ or $> 600,000\text{IU/mL}$) and self-reported race (black or non-black):

- PEG-IF alfa-2b at standard dose (1.5 micrograms/kg body weight/wk) in combination with PO RBV at a dose according to body weight (40–65kg, 800mg/d; > 65 –85kg, 1,000mg/d; > 85 –105kg, 1,200mg/d; and > 105 –125kg, 1,400mg/d);

- PEG-IFN- α 2b at a lower dose (1.0 microgram/kg body weight/wk) in combination with PO RBV (doses as above);
- PEG-IFN- α 2a at 180 micrograms/wk, plus PO RBV at 1,000–1,200mg/d per body weight (<75kg, 1,000mg/d; \geq 75kg, 1,200mg/d).

Primary endpoints: In IDEAL, insufficient virologic response at 12wk (detectable HCV RNA level and a decrease of $<2 \log_{10}$ IU from baseline) or at 24wk (detectable HCV RNA level) considered treatment failure, and therapy discontinued. In this GWAS, determinants of response, i.e. SVR, were primary endpoint.

Secondary endpoints: Rates of virologic response during treatment phase and relapse, defined as an undetectable HCV RNA level at the end of treatment, with a detectable HCV RNA level during F/U.

Follow-up: 24wk.

Results

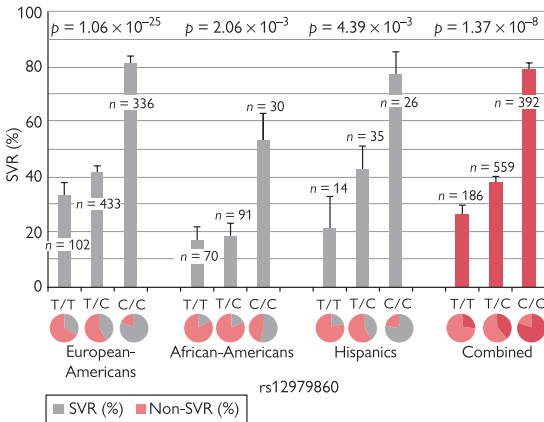


Fig. 13.1 Percentage of sustained virological response by genotypes of rs12979860.

Discussion

A polymorphism on chromosome 19, rs12979860, was strongly associated with SVR in all groups (see Fig. 13.1). The European-American population sample showed overwhelming genome-wide significance ($p = 1.06 \times 10^{-25}$). Combining p-values across the groups, the variant showed association at 1.37×10^{-28} . The polymorphism was 3 kilobases (kb) upstream of the *IL28B* gene encoding IFN-lambda-3 and explained much of the difference in response between European-American and African American patients. As the polymorphism appeared to associate with natural clearance, as well as treatment response, it seems likely that the gene product is involved in the innate control of HCV.

Problems

GWAS shows an association between markers and outcomes, in this case SVR. Further studies needed to show this is important prospectively to determine treatment choice and duration in different populations.

Neurology

- Introduction 348
- Stroke: care in dedicated units 350
- Ischaemic stroke: intravenous thrombolysis 352
- Transient ischaemic attack: urgent treatment 354
- Stroke: antiplatelet drugs 356
- Epilepsy: introduction of medication 358
- Epilepsy: withdrawal of medication 360
- Epilepsy: treatment of partial-onset epilepsy 362
- Epilepsy: treatment of generalized and unclassifiable epilepsy 364
- Migraine prophylaxis: topiramate 366
- Migraine treatment: sumatriptan 368
- Multiple sclerosis: steroids 370
- Multiple sclerosis: beta-interferon 372
- Parkinson's disease: early treatment 374
- Parkinson's disease: timing of levodopa 376
- Motor neuron disease: riluzole 378
- Guillain–Barré syndrome: intravenous immunoglobulin 380
- Peripheral neuropathy: gabapentin 382
- Bell's palsy: role of prednisolone and aciclovir 384

Introduction

‘[The neurologist is]...a brilliant and forgetful man with a bulging cranium, a loud bow tie, who reads Cicero in Latin for pleasure, hums Haydn sonatas, talks with ease about bits of the brain you’d forgotten existed, and—most importantly—never bothers about treatment.’

Richard Smith (BMJ Editor) 1999

While Richard Smith’s stereotypical description may still ring true for some people, the picture of neurology in the twenty-first century is clearly changing. Neurologists are moving from the ivory tower into more acute medicine; the intellectual challenge of making a diagnosis is greatly supported by more sophisticated investigation techniques, and treatment has become an important part of neurological management. Indeed, neurologists have been instrumental in designing and running RCTs of many therapies, including surgical treatments such as carotid endarterectomy.

Neurological diseases present particular challenges for trialists. Many are uncommon or rare, making recruitment difficult. The commoner ones, such as epilepsy, are very heterogeneous and thus may not be suited to trials of ‘one size fits all’ treatments. Many neurological disorders (e.g. multiple sclerosis (MS), Parkinson’s disease (PD)) cause increasing disability over many years, such that meaningful trials take time and will therefore be costly to run. This approach does not suit the powerful pharmaceutical industry well, which, simply put, needs to recoup its investment in the expensive business of developing new drugs as soon as possible. Thus, controversies abound about how truly effective some currently licensed treatments are (e.g. β -IFN for MS, or anti-CHEI for AD). Finally, agreeing upon easily measured and useful outcome measures is always a challenge—counting dead bodies is rarely relevant in neurological disorders, and measuring disability is fraught with difficulty.

Despite these problems, neurologists have met the challenge, as the trials in this chapter (and others) show. It is reassuring to know that, beyond making a diagnosis, neurologists now also have some treatments to offer to their patients. The last 10y in particular have seen an explosion of new therapies and investigative techniques for neurological disorders, and we now need to learn how best to use them.

Stroke: care in dedicated units

Alternative strategies for stroke care: a prospective randomised controlled trial.

AUTHORS: Kalra L, Evans E, Perez I et al.

REFERENCE: *Lancet* (2000) **356**, 894–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Post-stroke care in a dedicated stroke unit improves outcomes of death and dependency, compared to the general ward and domiciliary care.

Impact

Early admission to a specialized stroke unit is now universally regarded as best practice in the care of patients, following a stroke. This large RCT added weight to the evidence in favour of such organized inpatient care.

Aims

At the time that this trial was proposed, there was a growing body of evidence in favour of stroke unit care. However, up to 50% of stroke patients in the UK were cared for elsewhere, with some evidence to suggest equivalent outcomes in patients with organized care at home. This trial set out to compare best care on a dedicated stroke unit, on the general ward, and at home.

Methods

Patients: 457 patients from one region of the UK.

Inclusion criteria:

- Stroke as diagnosed by WHO criteria;
- Moderate severity, defined as persistent neurological deficit impairing mobility, continence, and ability to self-care;
- Onset of symptoms <72h.

Groups:

- Stroke unit care ($n = 152$; 148 confirmed strokes);
- Stroke team care on general ward ($n = 153$; 149 confirmed strokes);
- Domiciliary care ($n = 152$; 150 confirmed strokes).

Primary endpoint: Death or institutionalization at 1y.

Secondary endpoints: Dependence assessed by Modified Rankin Scale (0–3 = favourable outcome) and Barthel Index (15–20 = favourable outcome).

Follow-up: Outcomes assessed at 3, 6, and 12mo.

Results

Table 14.1 Summary of results

| At 12mo | Stroke unit | Stroke team | Home care | Unit vs team OR (95% CI) | Unit vs home OR (95% CI) | Team vs home OR (95% CI) |
|-----------------------------------|-------------|-------------|-----------|--------------------------|--------------------------|--------------------------|
| Mortality | 9% | 23% | 15% | 0.37 (0.21–0.66) | 0.59 (0.31–1.11) | 1.56 (0.96–2.53) |
| Institutionalization | 5% | 7% | 9% | 0.71 (0.29–1.72) | 0.58 (0.25–1.35) | 0.82 (0.38–1.75) |
| Mortality or institutionalization | 14% | 30% | 24% | 0.46 (0.30–0.72) | 0.59 (0.37–0.95) | 1.28 (0.87–1.87) |
| Modified Rankin 0–3 | 85% | 66% | 71% | 1.29 (1.13–1.47) | 1.21 (1.07–1.37) | 0.94 (0.81–1.09) |
| Barthel Index 15–20 | 87% | 69% | 71% | 1.27 (1.12–1.44) | 1.22 (1.09–1.37) | 0.97 (0.85–1.11) |

Discussion

This study showed significant advantage for specialized stroke unit care in the combined outcome of death or institutionalization at 12mo over either stroke team management on general wards or care at home. Regression analysis for baseline prognostic variables of age, Barthel Index, and dysphasia strengthened this effect, giving a risk of death or dependency at 1y 3.2 times greater (95% CI 1.6–6.4) for the stroke team patients, and 1.8 times greater (95% CI 1.1–3.8) for patients at home, than for the stroke unit patients. (See Table 14.1.)

Problems

Trials such as this have necessary limitations—the patients clearly cannot be blinded, and it is impossible to control for the inevitable human variability between medical and nursing teams in terms of application, engagement with patients, and assiduousness with basic care. However, the findings have been borne out by many other trials and meta-analyses.

Ischaemic stroke: intravenous thrombolysis

Tissue plasminogen activator for acute ischemic stroke.

AUTHORS: The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group.

REFERENCE: *N Engl J Med* (1995) 333;1581–87.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Thrombolysis with recombinant tissue plasminogen activator (r-tpa) within 3h of onset of acute ischaemic stroke (AIS) improves outcome at 3mo; this benefit outweighs the increased incidence of intracranial haemorrhage.

Impact

This study led to the widespread use of IV thrombolysis with r-tpa in the treatment of AIS. Since then, further studies have confirmed the benefit of thrombolysis up to 4.5h after symptom onset and its safety in a more general population—with the benefit highest the earlier r-tpa is given after symptom onset.

Aims

Previous open-label studies of thrombolysis for AIS had indicated that early treatment maximized benefit and reduced the risk of intracranial haemorrhage. This large-scale, randomized, placebo-controlled trial was designed to assess the risks and benefits of IV thrombolysis with r-tpa within 3h of onset of AIS.

Methods

Patients: 624 patients (291 in part 1; 333 in part 2) at multiple centres in the USA.

Inclusion criteria:

- AIS;
- Clearly defined time of onset;
- Neurological deficit measurable by the National Institutes of Health Stroke Scale (NIHSS);
- Intracranial haemorrhage excluded by CT imaging.

Groups:

- Part 1: 144 patients randomized to r-tpa; 147 to placebo;
- Part 2: 168 patients randomized to r-tpa; 165 to placebo.

Endpoints:

- Part 1: Improvement of neurological deficit at 24h: either complete resolution of deficit or improvement of ≥ 4 points on the NIHSS;

- Part 2: Minimal or no neurological deficit at 3mo. 'Favourable outcome': a score of 95 or 100 on the Barthel Index (0–100), 0 or 1 on the NIHSS, 0 or 1 on the Modified Rankin Scale, and 1 on the Glasgow Outcome Scale. These four outcome measures were combined into a global test statistic, giving an overall OR for favourable outcome.

Follow-up: Both groups were assessed at 24h and 3mo.

Results

- Part 1: At 24h after treatment, the proportion of patients with early clinical improvement did not differ between treatment groups;
- Part 2: Significantly more patients in the r-tpa groups had symptomatic (6.4% vs 0.7%) and fatal (2.9% vs 0.3%) intracranial haemorrhage in the first 36h after treatment. (See Table 14.2.)
- Mortality at 90d did not differ significantly between treatment groups: 54/312 (17%) r-tpa vs 64/312 (21%) placebo ($p = 0.30$).

Table 14.2 Summary of results

| Time from symptom onset to thrombolysis | OR (95% CI) for favourable outcome: r-tpa vs placebo | <i>p</i> |
|---|--|----------|
| 0–90min | 1.9 (1.2–2.9) | 0.005 |
| 91–180min | 1.9 (1.3–2.9) | 0.002 |

Discussion

Although there was no difference in clinical improvement at 24h, there was a clear advantage at 3mo, with r-tPA-treated patients being at least 30% more likely to have minimal or no disability. Since this study, IV thrombolysis has become one of the standard treatments for AIS. In 2008, the ECASS-3 study showed that IV r-tpa improved outcome in AIS 3–4.5h after onset (OR 1.34, 95% CI 1.02–1.76, $p = 0.04$). In 2012, the IST-3 was published as the largest study of IV r-tpa in AIS ≤ 6 h after onset and in patients excluded from previous studies, e.g. patients >80 y. The proportion of patients with a good outcome (Oxford Handicap Scale 0–2) was non-significantly increased in the r-tpa-group, with overall better outcomes (OR 1.27, 95% CI 1.10–1.47) for the r-tpa group in an ordinal shift analysis. The risk of intracranial haemorrhage and death within 7d was higher in the r-tpa group, but this was made up for by fewer deaths beyond that time. A meta-analysis of thrombolysis trials in AIS show improved outcomes with thrombolysis, with the most beneficial effects seen the earlier treatment is given.

Further reading

- Hacke W, Kaste M, Bluhmki E *et al.*; ECASS Investigators (2008). Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* **359**, 1317–29.
- IST-3 collaborative group, Sandercock P, Wardlaw JM, Lindley RI *et al.* (2012). The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [IST-3]): a randomised controlled trial. *Lancet* **379**, 2352–63.

Transient ischaemic attack: urgent treatment

EXPRESS study: Effect of urgent treatment of transient ischaemic attack and minor stroke on early recurrent stroke.

AUTHORS: Rothwell P, Giles M, Chandratheva A *et al.* (on behalf of the EXPRESS study).

REFERENCE: *Lancet* (2007) **370**, 1432–42.

STUDY DESIGN: Prospective cohort.

EVIDENCE LEVEL: 2a.

Key message

The risk of recurrence after a TIA and minor stroke is highest early after the event. Assessing patients rapidly and treating them urgently reduce the risk of early recurrence by 80%.

Impact

In the UK, where patients with TIA are often managed as outpatients, the results of this study have led to a restructuring of stroke and TIA services, with daily rapid-access TIA clinics now widely available.

Aims

The risk of early recurrence after a TIA and minor stroke is high. Modelling studies had suggested that early use of existing treatments could reduce this risk by 80–90%. THE EXPRESS study aimed to determine the effect of urgent treatment after TIA and minor stroke. The study was nested within a rigorous population-based incidence study of all TIA and stroke (Oxford Vascular Study, OXVASC), such that case ascertainment, investigation, and F/U were complete and identical in both periods.

Methods

Patient and inclusion criteria: 1,278 patients in OXVASC who presented with TIA or stroke.

Study phases

- In phase 1 of the study (2002–2004; $n = 634$), patients received appointments for the daily TIA clinic and were assessed, and management suggestions were faxed to their family doctor;
- In phase 2 (2004–2007; $n = 644$), patients seen without appointment, and treatment initiated in the clinic, i.e. time to assessment and treatment was reduced.

Primary outcome:

- Recurrent stroke within 90d of first presentation (assessed blind to study phase).

Results

- A total of 591 patients were ultimately referred to the study clinic during the study period;
- Clinical baseline characteristics did not differ significantly between study periods for either patient group.
- For patients attending the EXPRESS clinic between the study phases, there was:
 - No difference in delay between event and seeking medical attention;
 - Reduction in median (interquartile range, IQR) delay from seeking medical attention to clinic assessment: 3d (2–5) in phase 1 vs <1d (0–3) in phase 2 ($p < 0.0001$) (see Table 14.3);
 - Reduced median delay in prescribing treatment: 20d (8–53) vs 1d (0–3), $p < 0.0001$;
- The risk reduction applied equally to:
 - Men and women;
 - Patients presenting with TIA or minor stroke;
 - Patients of all ages.

Table 14.3 Summary of results

| | Phase 1 | Phase 2 | p |
|---------------------|----------------|---------------|---------|
| EXPRESS clinic | 32/310 (10.3%) | 6/281 (2.1%) | <0.0001 |
| Hospital-based care | 23/285 (8.1%) | 19/322 (5.9%) | 0.23 |

Discussion

Early initiation of existing treatments can prevent up to 80% of early recurrent strokes. The before/after methodology of this study is a different approach to that taken in a conventional RCT. The authors argue that, given the population-based cohort and the detailed prospective data collection, results are highly generalizable. The approach was more practical and ethical than randomization to early vs late treatment, and, as study groups did not differ in characteristics, other than the treatment protocol, the results should be valid. A number of different treatments (antiplatelet agents, antihypertensives, statins) were used, and it is not possible to say how much each aspect of the treatment approach contributed to the reduction in stroke risk.

Problems

- The study methodology of EXPRESS has been discussed widely, debating the acceptability and validity of the before/after approach. However, results were felt to be sufficiently compelling to lead to widespread changes in the running of TIA/minor stroke services in the UK.
- In some countries, all patients with TIA are admitted acutely and treated as inpatients. The EXPRESS results may be less relevant there but still emphasize the benefit of rapid treatment of TIA patients.
- EXPRESS was published concurrently with the SOS-TIA study (*Lancet Neurol* (2007) 6, 953–60), which studied an emergency round-the-clock access for TIA patients and estimated a similar risk reduction from rapid assessment, although it had no control group.

Stroke: antiplatelet drugs

Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke.

AUTHORS: Sacco RL, Diener HC, Yusuf S *et al.*; PROfESS Study Group.

REFERENCE: *N Engl J Med* (2008) **359**, 1238–51.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The efficacy of combination aspirin and dipyridamole and that of clopidogrel alone in the prevention of recurrent stroke is very similar, although non-inferiority criteria were not met.

Impact

Clopidogrel is now established as a standard treatment in the 2° prevention of stroke.

Aims

Antiplatelet drugs reduce the risk of recurrent stroke, with aspirin, clopidogrel, and the combination of aspirin plus extended-release dipyridamole (ASA-ERDP) all proven to be effective. Trials of both of the latter drug regimens had suggested superiority over aspirin, perhaps more so for ASA-ERDP. This Prevention Regimen for Effectively Avoiding Second Strokes (PROfESS) study aimed to compare the safety and efficacy of ASA-ERDP with that of clopidogrel in patients with recent ischaemic stroke.

Methods

Patients: 20,332 patients from 695 centres in 35 countries.

Inclusion criteria:

- Recent ischaemic stroke (<90d; amended to <120d plus at least two additional vascular risk factors later);
- Age ≥55y (amended to ≥50y later);
- Clinically and neurologically stable prior to randomization;
- No contraindications to the studied antiplatelet agents.

Design:

- Test for non-inferiority of ASA-ERDP vs clopidogrel; if confirmed, test for superiority.

Groups:

- Aspirin 25mg + ERDP 200mg bd (*n* = 10,181);
- Clopidogrel 75mg od (*n* = 10,151);
- Other groups (not reported): Telmisartan 80mg od; placebo.

Primary outcome: First recurrent stroke (ischaemic and haemorrhagic).

Secondary and tertiary outcomes:

- Secondary: Stroke, MI, or death;
- Tertiary: Haemorrhagic events (minor or major);

Follow up: Mean F/U 2.5y.

Results

Table 14.4 Summary of results

| | ASA-ERDP (n = 10,181) | Clopidogrel (n = 10,151) | HR (95% CI) for ASA-ERDP |
|--|--------------------------|-----------------------------|-----------------------------|
| Primary outcome: first recurrent stroke | 916 (9.0%) | 898 (8.8%) | 1.01 (0.92–1.11)* |
| Secondary outcome: stroke, MI, or vascular death | 1,333 (13.1%) | 1,333 (13.1%) | 0.99 (0.92–1.07) |
| Any haemorrhage | 535 (5.3%) | 494 (4.9%) | 1.08 (0.96–1.22) |
| Major haemorrhage | 419 (4.1%) | 365 (3.6%) | 1.15 (1.00–1.32) |
| Intracranial haemorrhage | 147 (1.4%) | 103 (1.0%) | 1.42 (1.11–1.83) |

*As the upper limit of the CI (1.11) extended beyond the prespecified non-inferiority margin of 1.075, non-inferiority criteria for the primary outcome were not met.

Discussion

Rates of recurrent events were very similar in both treatment groups. However, as the prespecified non-inferiority criteria were not met, it is not possible to say if either of the two drug regimens is superior to the other in 2° stroke prevention. Despite a higher risk of intracranial bleeding in the ASA-ERDP group, the net treatment benefit was similar in both groups. This trial is a good example of the effort required to try and find a difference between treatments and of the recent trend to try and show that one treatment, if not better, is at least not worse than (non-inferior to) another treatment. From a practical point of view, this trial has greatly contributed to ASA-ERDP and clopidogrel being used as equal options in 2° stroke prevention—with clopidogrel better tolerated and the advantage of once-per-day dosing. PROfESS looks at 2° stroke prevention in patients with a previous stroke; patients with TIA were not included. The efficacy of clopidogrel has not been shown in patients with previous TIA. As the ASA-ERDP trials (ESPS-2, ESPRIT) included TIA patients, some countries still only recommend ASA-ERDP in 2° prevention after TIA. Others regard the pathophysiology of ischaemic stroke and TIA as the same and use either clopidogrel or ASA-ERDP in both conditions. (See Table 14.4.)

Problems

The statistics for a non-inferiority study can seem arbitrary, especially the selection of the non-inferiority margin. The best way of doing this is still subject to discussion, even in statistical circles.

Further reading

Diener HC, Cunha L, Forbes C et al. (1996). European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* **143**, 1–13.
 ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ et al. (2006). Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet* **367**, 1665–73.

Epilepsy: introduction of medication

MESS (MRC Multicentre trial for Early epilepsy and Single Seizures) study: Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures.

AUTHORS: Marson A, Jacoby A, Johnson A *et al.*

REFERENCE: *Lancet* (2005) **365**, 2007–14.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The first large-scale randomized trial to provide data on the impact of early antiepileptic drug (AED) treatment on short-term seizure recurrence and long-term seizure freedom. Its findings suggest that, while effective in preventing early seizure recurrence, early treatment does not affect long-term seizure control.

Impact

The findings of this trial have aided the decision-making process for both clinician and patient when considering the introduction of antiepileptic medication in early epilepsy.

Aims

Recurrence rates of anywhere between 23% and 71% have been reported after a single first seizure. Considering the risks of treatment, as well as the variable natural history of the condition in individuals, it can be difficult to know when to commence AED treatment. This study aimed to compare the effects of policies of immediate and deferred drug treatment on early seizure recurrence and long-term seizure freedom in patients who presented with a single first seizure or with early epilepsy.

Methods

Patients: 1,443 patients from multiple international centres.

Inclusion criteria:

- Age >1mo;
- At least one clinically definite, unprovoked epileptic seizure;
- Both patient and clinician uncertain whether to introduce antiepileptic medication.

Exclusion criteria:

- Prior AED treatment;
- Progressive neurological disease.

Groups:

- Immediate treatment ($n = 722$): AED selected by clinician and started 'as soon as possible';
- Deferred treatment ($n = 721$): AED treatment withheld, until considered necessary by clinician and patient.

Primary outcomes:

- Time to first recurrent seizure of any type;
- Time to first recurrent tonic–clonic seizure;
- Time to second and fifth recurrent seizures of any type;
- Time to 2y remission;
- Proportion seizure-free for 2y: between 1 and 3y post-randomization, and between 3 and 5y post-randomization.

Secondary endpoints: Adverse events in each group.

Follow-up: At 3, 6, and 12mo, and yearly thereafter.

Results

Table 14.5 Summary of results

| | | 6mo | 2y | 5y | 8y | p |
|-------------------------------|---------------------|-----|-----|-----|-----|---------------|
| Time to 1st recurrent seizure | Immediate treatment | 22% | 37% | 48% | 52% | <0.0001 (all) |
| | Deferred treatment | 33% | 48% | 58% | 61% | – |
| Time to 5th recurrent seizure | Immediate treatment | 6% | 12% | 19% | 26% | 0.23 (all) |
| | Deferred treatment | 7% | 15% | 22% | 25% | – |
| Achieving 2y remission | Immediate treatment | – | 64% | 92% | 95% | 0.02 (at 2y) |
| | Deferred treatment | – | 52% | 90% | 96% | – |

Discussion

The findings of the trial clearly suggest that early treatment with AEDs prolongs the time to first and second recurrent seizures, and shortens the time to 2y remission. However, there was little difference between the two groups in longer-term seizure outcomes. Time to fifth seizure was similar in the immediate and deferred treatment groups, and the respective proportions achieving 2y seizure freedom at 5y and 8y were almost identical. This suggests that early treatment has little effect on long-term seizure control. (See Table 14.5.)

Problems

The trial was unmasked, and the absence of a placebo in the non-treatment group might be expected to increase the number of self-reported events, particularly the subtle symptoms of partial seizures. However, the figures for more objectively verifiable tonic–clonic seizures were similar to those for ‘any seizure’ and suggest that bias was not significant.

Epilepsy: withdrawal of medication

MRC Antiepileptic Drug Withdrawal Trial: Randomised study of antiepileptic drug withdrawal in patients in remission.

AUTHORS: MRC AED Withdrawal Study Group.

REFERENCE: *Lancet* (1991) **337**, 1175–80.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Withdrawal of AEDs in seizure-free patients is associated with an increased risk of seizure recurrence in the subsequent 2y. Thereafter, the risk becomes similar to that of patients remaining on treatment. The most important prognostic factors for seizure recurrence are a history of tonic-clonic seizures, the number of AEDs, and the duration of seizure freedom.

Impact

This large-scale trial provided the first reliable data to guide decision-making in AED withdrawal.

Aims

In most patients with epilepsy-associated seizures, treatment with AEDs leads to prompt remission of seizures. Despite both epilepsy and AED treatment being associated with medical risks, as well as social consequences, there had been no clear consensus as to when and how treatment should be withdrawn in those likely to remain seizure-free. This study aimed to compare the risks of seizure recurrence in patients with epilepsy in remission, by using either slow drug withdrawal or maintenance of therapy, and to identify important prognostic factors in seizure recurrence.

Methods

Patients: 1,013 patients from 40 centres in the UK and Europe. An additional 776 eligible, but non-randomized, patients were also followed up.

Inclusion criteria:

- Any age;
- ≥ 2 clinically definite partial or generalized epileptic seizures;
- Free of seizures for at least 2y;
- Taking ≥ 1 AEDs.

Exclusion criteria:

- Progressive neurological illness;
- Other condition likely to limit F/U to $< 2y$.

Groups:

- Slow drug withdrawal ($n = 510$): Rates of withdrawal for particular drugs prespecified, aiming for withdrawal over 6mo period;
- Continued drug therapy ($n = 503$): Maintained on existing doses, unless clinical indication to change.

Primary endpoint: time to first recurrent seizure (of any type) or last seizure-free F/U.

Secondary endpoints: time to first recurrent, generalized, tonic-clonic seizure.

Follow-up: At 3, 6, and 12mo, and yearly thereafter.

Results

Table 14.6 Summary of results

| | 0–6mo | 6–12mo | 18–24mo | 2–3y | 3–4y |
|-----------------|---------------|---------------|---------------|---------------|---------------|
| No withdrawal | 14% | 11% | 11% | 9% | 4% |
| Slow withdrawal | 40% | 37% | 14% | 6% | 3% |
| OR (95% CI) | 2.8 (1.8–4.3) | 3.4 (2.2–5.2) | 1.2 (0.6–2.2) | 0.6 (0.3–1.3) | 0.6 (0.1–2.5) |

Discussion

There was a significant increase in the risk of seizure recurrence in the first 2y after drug withdrawal. The most important prognostic factors for seizure recurrence were:

- A history of tonic-clonic seizures (whether 1° or 2°);
- Duration of seizure freedom at randomization (the shorter the period, the higher the risk of recurrence);
- The number of initial AEDs prescribed (the higher the number of drugs, the greater the risk of recurrence). (See Table 14.6.)

Problems

- Analysis in this trial was by ITT. The design allowed for changes to be made to ongoing drug therapy on the basis of clinical indication, and, in particular, children in the treatment group could withdraw from drugs after 1y. Overall, 35% of the treatment group withdrew during F/U.
- Although relatively large in scale, the trial detected few significant prognostic factors for seizure recurrence. A number of other factors seemed likely to be of prognostic value, but conclusions could not be drawn, due to wide CIs.

Epilepsy: treatment of partial-onset epilepsy

SANAD (Standard And New Antiepileptic Drugs) study—Arm A: The SANAD study of the effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy.

AUTHORS: SANAD Study Group.

REFERENCE: *Lancet* (2007) **369**, 1000–15.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Lamotrigine is better tolerated than, and superior or non-inferior in efficacy to, carbamazepine, the currently recommended first-line drug treatment of partial-onset seizures.

Impact

The study group recommended that there should be a reassessment of the NICE guidelines for first-line AED treatment of partial-onset seizures on the basis of the study findings.

Aims

Carbamazepine had been established as the first-line AED for patients with partial-onset seizures. This was based upon a previous meta-analysis of RCTs, which had demonstrated its relative efficacy over valproate. More recent RCTs had investigated the efficacy of several newer treatments; however, the methodology had not been ideal (e.g. due to short F/U), and results had been variable, with limited analysis of QoL variables. This large-scale, unblinded RCT was designed to assess the relative efficacy, tolerability, and cost-effectiveness of several newer AEDs, compared with carbamazepine.

Methods

Patients: 1,721 patients from multiple centres in the UK.

Inclusion criteria:

- Age >4y;
- Two clinically definite partial-onset seizures in the past 12mo;
- Not previously treated with a trial drug;
- Clinician judged carbamazepine to be a more appropriate standard treatment option than valproate.

Groups: Drug titration and maintenance dosage for all groups guided by treating clinician:

- Carbamazepine ($n = 378$);
- Gabapentin ($n = 377$);
- Lamotrigine ($n = 378$);
- Topiramate ($n = 378$);
- Oxcarbazepine ($n = 210$, drug introduced later during the trial).

Primary endpoints:

- Time from randomization to treatment failure (due to inadequate seizure control, intolerable SEs, or addition of a second drug);
- Time from randomization to first 12mo period of seizure freedom.

Secondary endpoints:

- Time from randomization to first seizure;
- Time to achieve 2y remission;
- Incidence of significant adverse events and SEs.

Follow-up: At 3 and 6mo, 1y, and annually thereafter. Drug dosage, seizures, hospital admissions, and adverse drug effects recorded.

Results

- **Time to treatment failure:** Expressed as overall percentage of patients remaining on drug. Lamotrigine proved superior to carbamazepine and to the other new AEDs at 6y F/U. Carbamazepine and topiramate were most frequently associated with withdrawal due to SEs, and gabapentin most frequently associated with withdrawal due to inadequate seizure control. Those taking carbamazepine were least likely to withdraw due to inadequate seizure control;
- **Time to 12mo seizure freedom:** ITT analysis showed carbamazepine to be superior to the newer AEDs. However, per-protocol comparison suggested 'non-inferiority' of lamotrigine and carbamazepine;
- **Time to first seizure and in time to 2y seizure freedom:** Carbamazepine was marginally superior to the newer drugs for both;
- **SEs:** 50% of patients reported SEs during the trial; differences between the drugs were small.

Discussion

This study demonstrated the superior or non-inferior efficacy of lamotrigine, compared with the standard first-line drug treatment, for partial-onset seizures. Additional cost analysis and QoL data suggested lamotrigine to be a viable alternative first-line therapy.

Problems

- The study was unblinded, due to cost implications, potential drug interactions, and practical difficulties of supplying dummy medications.
- Newer AEDs have come into common use, since the trial was designed, and were therefore not included. Of these, perhaps the most significant is levetiracetam, which is now a licensed monotherapy for partial and 2° generalized seizures, and an adjunctive therapy in juvenile myoclonic epilepsy.

Epilepsy: treatment of generalized and unclassifiable epilepsy

SANAD (Standard And New Antiepileptic Drugs) study—Arm B: The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy.

AUTHORS: SANAD study group.

REFERENCE: *Lancet* (2007) **369**, 1016–26.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Valproate should remain the drug of first choice for many patients with generalized epilepsy. It is more effective than lamotrigine and better tolerated than topiramate.

Impact

The first substantial evidence for efficacy and tolerability of valproate, in comparison to the newer AEDs, for the treatment of generalized epilepsy.

Aims

The relative efficacy of AEDs for generalized-onset seizures had been based upon a relatively poorer evidence base than that for partial-onset seizures. Despite valproate being established as the first-line treatment, a meta-analysis had found few differences between outcomes with this drug, compared with carbamazepine or phenytoin. This large-scale, unblinded RCT was designed to assess the relative efficacy, tolerability, and cost-effectiveness of the newer AEDs, compared to valproate, the current standard first-line treatment.

Methods

Patients: 716 patients from multiple centres in the UK.

Inclusion criteria:

- Age >4y;
- Two clinically definite, unprovoked generalized epileptic seizures in past 12mo;
- Valproate regarded by clinician to be better standard treatment than carbamazepine.

Groups: Drug titration and maintenance dosage for all groups, guided by treating clinician:

- Lamotrigine ($n = 239$);
- Topiramate ($n = 239$);
- Valproate ($n = 238$).

Primary endpoints:

- Time from randomization to treatment failure (inadequate seizure control or SEs);
- Time from randomization to first 12mo period of seizure freedom.

Secondary endpoints:

- Time from randomization to first seizure;
- Time from randomization to first 2y period of seizure freedom;
- Frequency of adverse effects.

Follow-up: At 3 and 6mo, 1y, and annually thereafter. Drug dosage, seizures, hospital admissions, and adverse drug effects recorded.

Results

- **Time to treatment failure (any reason):** Measured by cumulative incidence of treatment failure, valproate was superior to topiramate (HR 1.57, 95% CI 1.19–2.08), but not significantly superior to lamotrigine (HR 1.25, 95% CI 0.94–1.68). However, in post hoc analyses of subgroups with a diagnosis of generalized epilepsy (excluding unclassifiable epilepsy), valproate was significantly superior to both;
- **Time to treatment failure (adverse effects):** Topiramate was significantly inferior to both valproate (HR 1.55, 95% CI 1.07–2.26) and lamotrigine (HR 2.15, 95% CI 1.41–3.30), and lamotrigine was least likely to cause unacceptable SEs;
- **Time to treatment failure (inadequate seizure control):** Valproate was significantly superior to lamotrigine (HR 1.95, 95% CI 1.28–2.98), but its superiority over topiramate was not significant;
- **Time to 1y remission:** Valproate was significantly superior to lamotrigine (HR 0.76, 95% CI 0.62–0.94), but superiority over topiramate was not significant in the ITT analysis. However, per-protocol analysis suggested significant superiority of valproate over both lamotrigine and topiramate. The difference between these two analyses is likely to be due to patients switching to valproate, following treatment failure on topiramate;
- **Time to first seizure:** Valproate was superior to both lamotrigine and topiramate.

Discussion

For patients with generalized epilepsies, valproate was better than both lamotrigine and topiramate for time to treatment failure. It was superior to lamotrigine, but not to topiramate, for time to 1y remission. The current NICE and Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend valproate as the drug of first choice for generalized epilepsies, and, on the basis of the SANAD findings, this guidance remains unchanged.

Problems

- As with arm A, other AEDs have become available and widely used since the study and were not included. The SANAD-2 study tests levetiracetam and zonisamide with standard epilepsy treatments (sodium valproate, lamotrigine) and is ongoing.
- The issue of valproate teratogenicity remains a significant concern.

Migraine prophylaxis: topiramate

Topiramate in migraine prevention: results of a large controlled trial.

AUTHORS: Silberstein SD, Neto W, Schmitt J *et al.* for the MIGR-001 Study Group.

REFERENCE: *Arch Neurol* (2004) **61**, 490–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The largest randomized trial of an anticonvulsant in migraine prophylaxis.

Impact

In the UK, topiramate is the only anticonvulsant that has a licence for use in the prevention of migraine.

Aims

After several small and open-label studies had suggested efficacy of topiramate in migraine prevention, this randomized, double-blind, placebo-controlled, parallel-group multicentre study trial set out to evaluate the safety and efficacy of different doses of topiramate vs placebo in the prophylaxis of episodic migraine, according to the US Headache Consortium criteria for clinical studies.

Methods

Patients: 487 patients from multiple centres.

Inclusion criteria

- Age 12–65y;
- ≥6mo history of migraine, with or without aura;
- 3–12 attacks/mo.

Exclusion criteria

- Headache other than migraine;
- Previously failed >2 prophylactic treatments;
- Overuse of acute medication;
- Concurrent use of other migraine prophylactic agents.

Study design

- 14d washout period for prior prophylactics;
- 28d baseline phase off prophylactic medication, then randomization;
- 8wk titration period, 18wk maintenance phase;
- F/U every 4wk during double-blind phase.

Groups:

- 50mg/d topiramate ($n = 125$);
- 100mg/d topiramate ($n = 128$);
- 200 mg/d topiramate ($n = 117$);
- Placebo ($n = 117$).

Primary endpoint: Reduction in mean migraine frequency from baseline through double-blind phase.

Secondary endpoints

- Responder rate (proportion of patients with $\geq 50\%$ reduction in monthly migraine frequency);
- Mean change in monthly migraine days;
- Change in number of days per month requiring rescue medication.

Results

Of 487 patients randomized, 204 (42%) withdrew during the treatment phase (patient choice, lost to F/U, adverse events, lack of effect).

Primary endpoint: reduction in mean \pm SD monthly migraine frequency, compared to placebo (See Table 14.7.)

Table 14.7 Summary of results

| | Placebo | Topiramate 50mg | Topiramate 100mg | Topiramate 200mg |
|-----------|---------------|--------------------|---------------------|---------------------|
| Baseline | 5.6 ± 2.3 | 5.4 ± 2.4 | 5.4 ± 2.2 | 5.6 ± 2.6 |
| Treatment | 4.6 ± 3.0 | 4.1 ± 3.6 | 3.3 ± 2.9 | 3.3 ± 2.9 |
| <i>p</i> | | 0.24 | <0.001 | <0.001 |

Secondary endpoints:

- Responder rates ($\geq 50\%$ reduction in monthly migraine frequency), mean monthly migraine days, and use of rescue medication were all significantly improved for topiramate 100mg/d and 200mg/d, compared to placebo, but not for topiramate 50mg/d, which only showed a borderline significant increase in responder rate vs placebo;
- The commonest adverse effects included paraesthesiae, fatigue, anorexia, and nausea. These were slightly commoner in the 200mg/d group.

Discussion

The results suggest that topiramate at 100mg/d and 200mg/d is effective in preventing episodic migraine, with 50mg/d having little effect, and the use of 200mg/d perhaps hampered by more significant SEs. Results were consistent throughout multiple outcome measures.

Problems

- The high dropout rate makes the trial results difficult to generalize.
- The results show that topiramate is effective in episodic migraine, when compared to placebo. It does not tell us (as it was not set up to do so) how effective topiramate is, compared to other agents used, in migraine prophylaxis and if it also works in chronic migraine.

Migraine treatment: sumatriptan

Efficacy and safety of sumatriptan tablets (25mg, 50mg, and 100mg) in the acute treatment of migraine: defining the optimum doses of oral sumatriptan.

AUTHORS: Pfaffenrath V, Cunin G, Sjonell G *et al.*

REFERENCE: *Headache* (1998) **38**,184–90.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This was the first large, well-controlled trial sufficiently powered to compare different doses of oral sumatriptan. It showed that 50mg and 100mg doses are more effective than 25mg, and that the 50mg dose is associated with fewer adverse events than the 100mg dose.

Impact

Oral triptans are now the standard first-line treatment for migraine attacks. Sumatriptan is prescribed as a 50mg oral dose.

Aims

Previous studies had demonstrated the efficacy of SC and PO sumatriptan, compared to placebo, in treating acute migraine attacks. However, the relationship between efficacy and dose had not been adequately defined. This trial compared the efficacy and tolerability of three doses of sumatriptan, and the efficacy of a further dose of sumatriptan if migraine recurred within 24h.

Methods

Patients: 1,003 patients at 93 study sites in seven countries.

Inclusion criteria:

- Age 18–65y.
- 1–6 attacks/mo of moderate to severe migraine \pm aura by International Headache Society criteria over the previous 12mo.

Groups:

- First migraine attack: Placebo vs oral sumatriptan 25mg/50mg/100mg;
- Recurrence within 24h;
 - Patients on sumatriptan: Randomized to previous dose vs placebo;
 - Patients on placebo: 100mg of sumatriptan in case of recurrence.

Monitoring:

- Patients recorded the following symptoms on a diary card at 0.5, 1, 2, 3, and 4h after taking the study medication:
 - Headache severity on a 4-point scale (0 = none to 3 = severe);
 - Clinical disability (0 = none to 3 = requiring bed rest);
 - Presence of photo- and/or phonophobia, nausea, vomiting.

Primary endpoint: Proportion of patients with headache relief after the first treatment for the first attack, defined as reduction in pain intensity score from 2 or 3 to 0 or 1.

Secondary endpoints:

- Proportion with pain relief at each of the different time points and any of up to three treated attacks;
- Proportion with headache resolution;
- Proportion with resolution of clinical disability;
- Proportion with nausea, vomiting, photophobia;
- Proportion with adverse events.

Results

Primary endpoint: Proportion with pain relief. (See Table 14.8.)

Table 14.8 Summary of results

| | Placebo (n = 99) | 25mg (n = 303) | 50mg (n = 303) | 100mg (n = 298) |
|----|------------------|----------------|----------------|-----------------|
| 4h | 39% | 65% | 77% | 77% |

Each dose was significantly ($p < 0.05$) more effective than placebo, and the 50mg and 100mg doses were significantly more effective than the 25mg dose.

Secondary endpoints: Proportion with no pain. (See Table 14.9.)

Table 14.9 Summary of results

| | Placebo (n = 99) | 25mg (n = 303) | 50mg (n = 303) | 100mg (n = 298) |
|----|------------------|----------------|----------------|-----------------|
| 4h | 25% | 43% | 55% | 58% |

Each dose was significantly ($p < 0.05$) more effective than placebo, and the 50mg and 100mg doses were significantly more effective than the 25mg dose.

- Of the 827 patients treating three attacks, 81%, 81%, 67%, and 40% in the 100mg, 50mg, and 25mg sumatriptan, and placebo groups had headache relief 4h post-dose for at least two out of three attacks ($p < 0.05$ vs placebo);
- The 100mg and 50mg doses were more effective at reducing photo-/phonophobia and clinical disability 4h post-dose than 25mg ($p < 0.05$);
- Relief of recurrent headache 2h after the second dose of study medication occurred in greater percentages of patients using sumatriptan (any dose) than in those using placebo;
- The incidence of adverse events with sumatriptan 25mg and 50mg was similar to placebo and lower than with sumatriptan 100mg.

Discussion

In this study, the 50mg dose of sumatriptan offered the best balance of efficacy and SE profile. The efficacy of sumatriptan was maintained over repeated attacks, and it was also effective in cases of early recurrent headache. Sumatriptan was the first triptan drug. Others have followed in a variety of doses and formulations. For a comprehensive review of currently available triptans, see *Cephalalgia* (2002) 22, 633–58.

Problems

- Oral treatment is not possible in all patients, and, in those suffering from severe nausea/vomiting early in the attack, an alternative route (nasal spray, SC injection, orodispersible tablets) should be used;
- All triptan preparations are considerably more expensive than simple analgesic medications, and, given the high prevalence of migraine in the population, they come at a significant financial cost.

Multiple sclerosis: steroids

Double-blind, randomized, placebo-controlled study of oral, high-dose methylprednisolone in attacks of MS.

AUTHORS: Sellebjerg F, Frederiksen J, Nielsen P *et al.*

REFERENCE: *Neurology* (1998) **51**, 529–34.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The first RCT to demonstrate the efficacy of PO steroid treatment in attacks of MS.

Impact

PO steroid administration is widely used as an easier and cheaper alternative to the IV route in the treatment of MS relapses.

Aims

Previous trials had demonstrated the efficacy of high-dose IV methylprednisolone in the management of attacks of MS but suggested that intermediate-dose PO steroids were no more effective than placebo. This trial set out to assess the efficacy of high-dose PO steroid treatment in acute MS relapses.

Methods

Patients: 51 patients at one centre in Denmark.

Inclusion criteria:

- Age 18–59y;
- Relapsing–remitting MS;
- MS relapse: defined as new or recurrent previous symptoms of duration >24h and <4wk in the absence of systemic infection.

Groups:

- PO methylprednisolone 500mg for 5d, followed by 10d of tapered withdrawal ($n = 26$);
- Placebo of identical appearance ($n = 25$).

Primary endpoints:

- Scripps Neurological Rating Scale (SNRS; minimum score –10, maximum score 100; higher score means better function) at 1 and 3wk. Covariate analysis with baseline values;
- Patient assessment of symptom severity on visual analogue scale (VAS) at 1 and 3wk. Covariate analysis with baseline values;
- Change in SNRS between baseline and 8wk;
- Patient-subjective assessment of treatment, determined by efficacy questionnaire.

Secondary endpoints:

- Response to treatment at 1, 3, and 8wk, defined as at least 1-point improvement on the Kurtzke Expanded Disability Status Scale (EDSS);
- Change in SNRS and VAS at individual visits.

Follow-up: Patients assessed before treatment and after 1, 3, and 8wk of treatment. Thereafter, patients reviewed at the onset of a new attack occurring within up to 1y of F/U.

Results

Table 14.10 SNRS (increase = improvement)

| | Baseline score | Score improvement (range) | | |
|--------------------|----------------|---------------------------|--------------|--------------|
| | | At 1wk | At 3wk | At 8wk |
| Methylprednisolone | 75 (55–83) | 5 (2–8) | 8 (3–12) | 11 (3–15) |
| Placebo | 69 (65–77) | 1 (–1 to +3) | 1 (–1 to +8) | 0 (–5 to +6) |
| <i>p</i> | ns | 0.006 | 0.01 | 0.0007 |

Table 14.11 VAS (increase = improvement)

| | Baseline score | Score improvement (range) | | |
|--------------------|----------------|---------------------------|----------------|--------------|
| | | At 1wk | At 3wk | At 8wk |
| Methylprednisolone | 71 (50–80) | 4 (2–19) | 15 (–1 to +24) | 19 (6–26) |
| Placebo | 67 (48–82) | 1 (–8 to +7) | 4 (–5 to +11) | 0 (–5 to +6) |
| <i>p</i> | ns | 0.03 | 0.06 | 0.0007 |

Note: figures in brackets represent the interquartile range.

- The difference in scores on the efficacy questionnaire at 8wk only reached statistical significance at the level required for a 2° efficacy measure ($p < 0.05$, whereas $p < 0.0125$ required in the ITT for primary outcome measures). (See Tables 14.10 and 14.11.)
- The number of ‘responders’ after 1, 3, and 8wk, respectively, as judged by the change in EDSS, was significantly greater in the treatment group (8, 14, and 17) than the placebo group (1, 6, and 8).

Discussion

Previous trials had shown the efficacy of high-dose IV methylprednisolone vs placebo, and some small-scale trial evidence suggested similar efficacy of PO, compared with IV, administration. However, this trial provided the first clear evidence of the superiority of high-dose PO steroids over placebo in MS relapse. High-dose PO methylprednisolone is once more being widely used as an alternative to the IV route. Methylprednisolone 500mg is equivalent to prednisolone 625mg or dexamethasone 94mg.

Subsequent trials (e.g. *Lancet* (1997) 349, 902–6) directly compared IV vs PO high-dose methylprednisolone and found no significant difference in efficacy, further supporting the use of PO steroids in the treatment of acute MS relapses.

Problems

- The main limitations of the trial are small study numbers and an excess of SEs in the treatment group. This almost certainly introduced some unblinding and may have influenced the self-reported outcomes.

Multiple sclerosis: beta-interferon

PRISMS (Prevention of Relapses and disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) study: Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis.

AUTHORS: PRISMS Study Group.

REFERENCE: *Lancet* (1998) **352**, 1498–504.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

SC IFN- β -1a reduces relapse frequency and disease progression over a 2y period in patients with MS.

Impact

IFN- β -1a is now widely used in patients with early MS and frequent relapses.

Aims

Earlier trials had suggested efficacy of IFN- β in the short-term reduction of relapse rate and MRI lesion load in relapsing–remitting MS. However, evidence of efficacy had not been universally accepted, due to the use of different types of IFN- β and a lack of clarity of the significance of the results. This trial set out to definitively determine the effect of SC IFN- β at two different doses in preventing relapse and limiting clinical progression of MS over a 2y period.

Methods

Patients: 560 patients at 22 centres in nine countries.

Inclusion criteria:

- Adult;
- Clinically or laboratory-supported definite MS of >1y duration;
- Two relapses in past 2y;
- Kurtzke EDSS score 0–5 (where a higher score indicates greater disability).

Groups: All administered by SC injection 3× weekly:

- IFN- β -1a 22 micrograms (6MU) ($n = 189$);
- IFN- β -1a 44 micrograms (12MU) ($n = 184$);
- Placebo ($n = 187$).

Primary endpoint: Number of relapses during study.

Secondary endpoints:

- Time to first and second relapse;
- Proportion of relapse-free patients;
- Progression of disability defined as 1-point increase on EDSS;
- Ambulation index;
- Arm function index;
- Requirement for hospital admission and steroid treatment;
- MRI findings.

Follow-up:

- Neurological assessment every 3mo and within 48h of MRI scans; MRI twice yearly in all patients;
- Monthly MRI for first 9mo of trial in 205 patients.

Results**Table 14.12** Summary of results

| | Placebo | IFN (22 micrograms) | IFN (44 micrograms) |
|------------------------|---------|---------------------|---------------------|
| Relapses | 2.56 | 1.82 | 1.73 |
| % reduction vs placebo | — | 27 (14–39) | 33 (21–44) |
| % relapse-free at 2y | 16 | 27 | 32 |
| OR (none vs any) | 1.00 | 2.01 (1.21–3.21) | 2.57 (1.56–2.45) |

Figures in brackets are 95% CIs.

- Median time to first relapse was increased by 3mo in the 22 micrograms, and by 5mo in the 44 micrograms, treatment groups, compared with placebo;
- Time to sustained progression was prolonged by 6.5mo in the 22 micrograms, and by 9.4mo in the 44 micrograms, treatment groups. In patients with more severe disease, time to progression was only prolonged in the 44 micrograms treatment group (see Table 14.12);
- The median total MRI lesion load was increased by 11% in the placebo group. Median lesion load decreased by 1% in the 22 micrograms, and by 4% in the 44 micrograms, treatment groups.

Discussion

This early IFN trial suggested significant benefits, in terms of relapse prevention and delayed longer-term disease progression. A 2001 Cochrane review of the evidence for recombinant IFN in MS reported an overall reduction in relapse rate (RR 0.80, 95% CI 0.73–0.88) and disease progression (RR 0.69, 95% CI 0.55–0.87) at 2y. However, significant doubt was expressed over the strength of these results with regard to the number, assignment, and (unknown) clinical course of patients withdrawing from the trials. If all IFN-treated withdrawals suffered from disease progression, the evidence that IFN prevents progression was no longer present.

In 2002, NICE appraisal of IFN- β and glatiramer acetate for the treatment of MS reported that neither agent could be recommended on the basis of clinical and cost-effectiveness. This led to the 'risk sharing scheme' between the manufacturers and the Department of Health for the supply of IFN- β and glatiramer acetate to the NHS, which is set to end in 2015.

In recent years, further disease-modifying drugs for MS have been licensed, among which are natalizumab, a monoclonal antibody, and fingolimod, one of the first PO disease-modifying drugs.

Parkinson's disease: early treatment

A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa.

AUTHORS: Rascol O, Brooks D, Korczyn A *et al.*

REFERENCE: *N Engl J Med* (2000) **342**, 1484–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

One of several RCTs to show a significantly reduced risk of dyskinesia in patients treated with a dopamine agonist, compared to those treated with levodopa (L-dopa) in early PD.

Impact

The trial supported the use of dopamine agonists as initial treatment for early PD.

Aims

This study aimed to resolve the long-standing controversy as to whether L-dopa or a dopamine agonist should be the standard initial therapy in early PD, with particular reference to the incidence of treatment-induced dyskinesia. The trial also aimed to compare the efficacy and tolerability of the two drugs.

Methods

Patients: 268 patients at 30 centres in Europe, Israel, and Canada.

Inclusion criteria:

- Age ≥ 30 y;
- Clinical diagnosis of PD;
- Hoehn–Yahr stages 1–3 (unilateral early disease—more advanced bilateral disease);
- Requiring dopaminergic therapy;
- Maximum duration of prior treatment 6wk;
- Dopaminergic medication withdrawn 2wk before entry.

Groups: Open-label addition of L-dopa available to patients in both groups, if inadequate control on maximal doses of either study drug:

- Ropinirole treatment: Introduced at 0.75mg/d. Dose increments at weekly intervals, according to clinical requirement, to maximum 24mg/d ($n = 179$; two with dyskinesia at baseline);
- Levodopa (+ benserazide) treatment: Introduced at 50mg/d. Dose increments at weekly intervals, according to clinical requirement, to maximum 1,200mg/d ($n = 89$; one with dyskinesia at baseline).

Primary outcome: Development of dyskinesia.

Secondary outcomes:

- Development of disabling dyskinesia;
- Measures of ADLs;
- Measures of motor function;
- 'Wearing off' with increasing symptom severity at end of dose;
- All primary and secondary outcomes assessed by means of the UPDRS (Unified Parkinson's Disease Rating Scale).

Follow-up: At weekly intervals for the first month, fortnightly for the next 2mo, monthly for the next 6mo, and every 2mo thereafter.

Results

- A total of 85 patients (47%) in the ropinirole group and 45 patients in the L-dopa group (51%) completed the study;
- Of these, 56 patients (66%) in the ropinirole group and 16 patients (35%) in the L-dopa group received open-label supplementary L-dopa;
- A total of 36/177 patients (20%) in the ropinirole group and 40/88 patients (45%) in the L-dopa group developed dyskinesia over the 5y F/U period;
- Before introduction of open-label L-dopa, nine of 177 patients (5%) in the ropinirole group and 32 of 88 patients (36%) receiving L-dopa had developed dyskinesia;
- Changes in mean UPDRS scores for ADLs did not differ significantly between the groups;
- There was a small, but significant, difference in the change from baseline in UPDRS motor scores between the two groups, with L-dopa conferring a 4.5 point advantage (on a point score range of 0–108, 95% CI 1.25–7.72).

Discussion

Initial treatment of early PD with the dopamine agonist ropinirole significantly reduced the risk of developing dyskinesia, compared to initial treatment with L-dopa. Other motor complications were not significantly reduced in the ropinirole group. This effect on dyskinesia may reflect the difference in the half-life between L-dopa (1.5–2h) and ropinirole (6–8h), with L-dopa giving pulsatile, and ropinirole more continuous, dopamine receptor stimulation.

Problems

- The dropout rate in this trial was very high, with less than half of the randomized patients completing the study.
- Late motor complications may be a sign of progressive disease and degeneration of dopamine neurons, rather than only an effect of L-dopa administration.
- While associated with more dyskinesia, several studies have shown that L-dopa is the most effective drug to reduce motor symptoms of PD and may also slow down its progression.
- The decision of how to treat a patient with early PD has to be individualized and needs to take into account the patient's age and severity of symptoms. Younger patients often progress more quickly but are also more likely to develop dyskinesia—they are often initially started on a dopamine agonist, but more rapid disease progression may require early use of L-dopa for adequate symptom control.

Parkinson's disease: timing of levodopa

ELLDOPA (Early vs Late LevoDOPA) study: Levodopa and the progression of Parkinson's disease.

AUTHORS: Fahn S *et al.*, and the Parkinson's Study Group.

REFERENCE: *N Engl J Med* (2004) **351**, 2498–508.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

L-dopa does not accelerate, and may indeed slow, the rate of decline in PD.

Impact

It has been common practice in the treatment of idiopathic PD to delay the introduction of L-dopa for as long as possible, due to a belief that the drug is the cause of motor fluctuations and may accelerate disease progression. This practice was challenged by the findings of the ELLDOPA study.

Aims

The dopamine precursor L-dopa remains the most effective treatment for the symptoms of idiopathic PD. *In vitro* studies and more recent functional neuroimaging in PD patients have suggested that L-dopa might have a neurotoxic effect, further depleting the remaining dopaminergic neurons. This study set out to assess whether treatment with L-dopa caused accelerated clinical decline, compared with placebo.

Methods

Patients: 361 patients at 33 centres in the USA and five in Canada.

Inclusion criteria: Early idiopathic PD:

- >30y old;
- Diagnosed <2y previously;
- Unilateral or mild bilateral disease;
- Not on treatment and judged unlikely to require treatment within 9mo.

Groups: Double blind randomization:

- Placebo ($n = 90$);
- Carbidopa/L-dopa 12.5/50mg tds ($n = 92$);
- Carbidopa/L-dopa 50/100mg tds ($n = 88$);
- Carbidopa/L-dopa 100/200mg tds ($n = 91$);
- 40wk treatment, including 9wk blinded dose titration, followed by medication withdrawal and 2wk 'washout' period.

Primary outcome: Change in PD severity between baseline and wk 42 (2wk after withdrawal of study drug), as assessed by the total score on the UPDRS.

Secondary outcome: Change in total UPDRS score at interim F/U visits.

Follow-up: At screening, baseline, and at wk 3, 9, 24, 40, 41, and 42.

Results

Table 14.13 Summary of results

| | Placebo | L-dopa 150mg | L-dopa 300mg | L-dopa 600mg | p |
|---|---------------|-----------------|-----------------|-----------------|-----------------------|
| Change in UPDRS from baseline to 42wk (mean \pm SD) | 7.8 \pm 9.0 | 1.9 \pm 6.0 | 1.9 \pm 6.9 | -1.4 \pm 7.7 | <0.001 (all doses) |

- In addition to the overall slowing of deterioration among those taking L-dopa, compared to the placebo group, there was a strong dose–response relationship beginning at wk 9 (following dose titration) (see Table 14.13);
- Those taking 600mg L-dopa daily had lower UPDRS scores both during the treatment phase and after washout than those taking 300mg who, in turn, fared better than those taking 150mg.

Discussion

Although not one of the stated aims of the trial, the interim treatment phase data did provide confirmation of the effectiveness of L-dopa as a treatment for symptoms in idiopathic PD, as compared to placebo. This had not been previously demonstrated in an RCT. Within the relatively short timescale of the trial, the primary outcome data suggest that L-dopa does not accelerate decline in early PD. The difference in UPDRS scores between treatment and placebo groups after washout could reflect either a prolonged therapeutic effect or a neuroprotective effect of L-dopa. The possibility that the washout period was simply too short and that L-dopa was still having a therapeutic effect at the final assessment was considered. A small group of patients continued the washout period to 4wk; no further decline was observed, but the group was too small for these results to be meaningfully interpreted. An imaging substudy of ELLDOPA in 116 patients showed that L-dopa was associated with a greater decline of basal ganglia uptake of dopamine. This may indicate that L-dopa accelerates the loss of nigrostriatal dopamine nerve terminals or that its effects modify the dopamine transporter.

Problems

- The clinical course of idiopathic PD is long, often spanning decades. The trial duration of 9.5mo is short, and it is not clear that these results can be extrapolated to the longer term.
- The clinical findings and the findings of the imaging substudy are potentially conflicting, and the imaging findings may indicate an L-dopa-induced toxic effect on dopamine neurons. Any potential long-term effects of L-dopa in PD remain uncertain.

Motor neuron disease: riluzole

A controlled trial of riluzole in amyotrophic lateral sclerosis.

AUTHORS: Bensimon G, Lacomblez L, Meininger V.

REFERENCE: *N Engl J Med* (1994) **330**, 585–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Riluzole slows the progression of amyotrophic lateral sclerosis (ALS) and prolongs survival in patients with bulbar-onset disease.

Impact

Riluzole is the first treatment approved for ALS. It is approved by UK NICE, although its cost-effectiveness remains controversial.

Aims

The pathogenesis of ALS remains unclear. It is a progressive and universally fatal neurodegenerative condition, with a median survival from diagnosis of 37–49mo. Glutamate-mediated excitotoxicity has been mooted as an underlying cause, and therefore drugs that modulate glutamatergic transmission had been proposed as potential therapeutic agents. This study aimed to evaluate the efficacy and safety of the ant glutamate agent riluzole.

Methods

Patients: 155 patients at seven centres in France.

Inclusion criteria:

- Clinically probable or definite ALS;
- Age 20–75y;
- 5y or less from symptom onset;
- Forced vital capacity (FVC) >60% predicted;
- No evidence of conduction block on nerve conduction studies.

Groups: Patients stratified, according to limb or bulbar onset of disease:

- Riluzole: 100mg od ($n = 77$; 62 limb onset, 15 bulbar onset);
- Placebo ($n = 78$; 61 limb onset, 17 bulbar onset).

Primary endpoint: Survival and change in functional status after 12mo of treatment.

Secondary endpoints:

- Change in muscle power (22 muscle groups, MRC grading);
- Respiratory function (FVC);
- Clinical Global Impression of Change scale (CGIC);
- Patient assessment of fasciculations, cramps, stiffness, and tiredness (VAS).

Follow-up: Every 2mo from study entry. Functional status assessed at each visit (limb and bulbar function evaluated by modified Norris scales, clinical examination, and symptoms reported by patient).

Results

Table 14.14 Summary of results

| | Riluzole | Placebo | <i>p</i> |
|---------------------|---------------|---------------|----------|
| <i>All patients</i> | <i>n = 77</i> | <i>n = 78</i> | |
| Alive at 12mo | 57 (74%) | 45 (58%) | 0.01 |
| <i>Bulbar onset</i> | <i>n = 15</i> | <i>n = 17</i> | |
| Alive at 12mo | 11 (73%) | 6 (35%) | 0.01 |
| <i>Limb onset</i> | <i>n = 62</i> | <i>n = 61</i> | |
| Alive at 12mo | 46 (74%) | 39 (64%) | 0.17 |

- Overall median survival = 449d (placebo) and 532d (riluzole);
- Among the bulbar-onset patients, median survival = 239d (placebo) and 'not yet been reached after 476d of F/U' (riluzole) (see Table 14.14);
- Rates of decline in functional assessment scores were only significantly different for measures of muscle power (33% reduction in rate of deterioration over 12mo, $p = 0.03$).

Discussion

Riluzole appeared to slow the rate of deterioration and prolong survival in patients with ALS. However, this effect was only significant in patients with bulbar-onset disease. Patients with limb-onset disease showed only a non-significant trend towards benefit. Therefore, it is perhaps surprising that, in terms of specific functional assessment, the only significant effect appeared to be on the rate of progression of limb muscle weakness. The effect on rate of deterioration of bulbar function was not significant.

A more recent (2007) Cochrane review of riluzole in ALS suggested a 2–3mo increase in median survival, compared with placebo. The use of riluzole in ALS has been approved by UK NICE, but its cost-effectiveness remains controversial, with estimates of cost per QALY ranging from £18,000 to £43,000.

Guillain–Barré syndrome: intravenous immunoglobulin

Randomised trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain–Barré syndrome.

AUTHORS: Plasma Exchange/Sandoglobulin Guillain–Barré Syndrome Trial Group.

REFERENCE: *Lancet* (1997) **349**, 225–30.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The biggest randomized trial to show that intravenous immunoglobulin (IVIG) is at least as effective as plasma exchange (PE) in the treatment of acute Guillain–Barré syndrome (GBS).

Impact

IVIG is now the standard treatment in patients with severe GBS.

Aims

Prior to this study, several trials had shown that PE improved outcome in GBS. IVIG is more convenient to use and may be safer than PE. One trial (*N Engl J Med* (1992) **326**, 1123–9) had suggested that IVIG and PE were similarly effective in the treatment of GBS, but it was relatively small, and there was persisting uncertainty. The current trial aimed to determine if IVIG was equivalent or superior to PE in the treatment of GBS, and if PE followed by IVIG was superior to the better single treatment.

Methods

Patients: 379 patients from multiple centres in 11 countries.

Inclusion criteria:

- Diagnosis of GBS made by a qualified neurologist with satisfaction of accepted clinical and CSF criteria;
- Age >16y;
- Severe disease (requiring aid to walk or worse).

Exclusion criteria:

- Atypical GBS;
- Serious pre-existing other illness;
- Contraindication to PE or IVIG.

Groups:

- PE ($n = 121$): five 50mL/kg exchanges, to achieve a total exchange of 250mL/kg, completed within 8–13d after randomization;
- IVIG ($n = 130$): human Ig 0.4mg/kg daily for 5d, starting on the day of randomization;
- PE followed by IVIG ($n = 128$): PE as above, followed by IVIG, starting the day after completion of PE.

Treatment had to be started within 8h of randomization.

Follow-up: Disability grade (0–6; 0 = no abnormality), arm grade (0–5), and vital capacity were assessed at randomization, and after 2, 4, 8, 12, and 24wk.

Primary outcome: Disability grade after 4wk. Two treatments seen as equivalent, if the 95% CI of the difference in the mean improvement excluded a true difference of >0.5 grade.

Secondary outcomes:

- Time from randomization to unaided walking;
- Time to permanent discontinuation from artificial ventilation;
- Rate of recovery: changes in disability grade over 48wk F/U.

Results

Table 14.15 Summary of results

| | PE | IVIG | PE + IVIG |
|--|-----------|-----------|-----------|
| Mean (SD) change in disability grade after 4wk | 0.9 (1.3) | 0.8 (1.3) | 1.1 (1.4) |

Difference between treatments:

- PE vs IVIG: 0.09 (95% CI −0.23 to 0.42); criterion for equivalence met;
- PE + IVIG vs IVIG alone: 0.29 (−0.04 to 0.63); equivalence not met;
- PE + IVIG vs PE alone: 0.20 (−0.14 to 0.54); equivalence not met;
- None of the secondary outcome measures differed significantly between treatment groups, although, for some of them, there was a trend for better outcome in the combined treatment group;
- Fewer patients received <75% of their treatment in the IVIG group (2.3%) vs the PE group (13.8%). (See Table 14.15.)

Discussion

Similar cost and outcome, but greater simplicity and better tolerability may make IVIG preferable over PE in the treatment of GBS. Outcomes may be slightly better with combined treatment, but not to an extent that would justify the greater inconvenience, cost, and risks.

Problems

- There are no good-quality studies testing IVIG vs placebo. This is because, by the time it came into use, PE was regarded as the standard treatment, and comparing to placebo would have been unethical;
- Because it is a human blood product, IVIG may carry long-term infective risks not yet recognized, although current data suggest its use is safe;
- The availability of IVIG depends on sufficient blood supplies, and, with its expanding use also for other conditions, shortages in supply have already occurred.

Peripheral neuropathy: gabapentin

Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial.

AUTHORS: Backonja M, Beydoun A, Edwards K et al.

REFERENCE: JAMA (1998) 280, 1831–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Gabapentin significantly improves neuropathic pain and associated sleep disturbance in patients with diabetic neuropathy.

Impact

Gabapentin is now widely used in the treatment of many forms of neuropathic pain—not just in patients with diabetic neuropathy.

Aims

Diabetic neuropathy can cause severe pain and is associated with sleep and mood disturbances. Its progress can be modified by improved glycaemic control. This trial aimed to assess the efficacy of gabapentin in the treatment of pain associated with diabetic peripheral neuropathy.

Methods

Patients: 165 patients at multiple centres across the USA.

Inclusion criteria:

- Type 1 or 2 DM;
- Pain attributed to peripheral neuropathy of 1–5y duration;
- Pain rating score of at least 40mm on 100mm VAS of the Short Form McGill Pain Questionnaire (SF-MPQ).

Groups:

- Gabapentin: 4wk titration phase to max. 3,600mg od, followed by 4wk fixed-dose period at maximum tolerated dose ($n = 84$);
- Placebo: Identical capsules ($n = 81$).

Primary endpoint: Pain severity rating (range 0–10), recorded in daily diaries by using the 11-point Likert scale.

Secondary endpoints:

- SF-MPQ scores;
- Weekly mean sleep interference scores;
- Patient Global Impression of Change (PGIC);
- CGIC.

Follow-up:

- Wk 2 and 4: SF-MPQ completed;
- Wk 8: SF-MPQ, Short-form 36 Quality of Life Questionnaire (SF-36 QoL), and Profile of Mood States (POMS) completed.

Results

Primary outcome measure:

Table 14.16 Summary of results

| | Gabapentin | | Placebo | | <i>p</i> |
|-----------------|------------|------|----------|------|----------|
| | Baseline | Wk 8 | Baseline | Wk 8 | |
| Mean pain score | 6.4 | 3.9 | 6.5 | 5.1 | <0.001 |

Secondary outcome measures:

- Similar modest, but significant, differences were seen in the secondary outcome measures;
- Mean sleep interference scores (0–10) differed by 1.5 in favour of gabapentin ($p = 0.001$);
- In the SF-MPQ total pain scores (0–45), there was a 6-point difference in favour of gabapentin ($p = 0.001$);
- In the SF-MPQ VAS (100mm), there was a 17mm difference in favour of gabapentin ($p = 0.001$);
- In the SF-MPQ present pain intensity scores (0–5), there was a 0.6-point difference in favour of gabapentin ($p < 0.001$);
- Patients had significantly greater improvement in pain with gabapentin, as compared with placebo, on both PGIC and CGIC scales. (See Table 14.16.)

Discussion

While gabapentin was initially promoted as an AED, it has not been particularly successful as an anticonvulsant (see also SANAD study on partial epilepsy) but is now a standard drug in the treatment of neuropathic pain. This trial demonstrated modest, but significant, efficacy of gabapentin in the treatment of pain associated with diabetic neuropathy. A variety of other agents have efficacy in controlling neuropathic pain, including tricyclic antidepressants (TCAs), the serotonin/noradrenaline reuptake inhibitor (SNRI) duloxetine, and the newer AED pregabalin.

Problems

- Diabetes is a common cause of painful peripheral neuropathy, and restriction of the trial to this group produced a relatively homogeneous study population. It does not, of course, necessarily follow that all neuropathic pain will respond in the same way, but this has been widely assumed.
- The benefits of gabapentin demonstrated in this trial are of similar order to those of TCA drugs such as amitriptyline.

Bell's palsy: role of prednisolone and aciclovir

Early treatment with prednisolone or acyclovir in Bell's palsy.

AUTHORS: Sullivan F, Swan I, Donnan P et al.

REFERENCE: *N Engl J Med* (2007) 357, 1598–607.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

When prescribed within the first 3d of symptom onset of Bell's palsy, complete recovery of facial function is more likely, following treatment with prednisolone vs placebo. There is no added benefit of combining prednisolone with aciclovir.

Impact

This adequately powered study confirmed the previously held opinion that prednisolone is beneficial in treating Bell's palsy. As such, all patients should receive this treatment early (within 3d of symptom onset). For patients with risk factors for systemic steroid use, reassurance can be offered that around 85% will recover without treatment.

Aims

Bell's palsy has been proposed to have an association with HSV. Corticosteroid treatment has been widely regarded as effective in improving prognosis. Antiviral agents, such as aciclovir, are also used; however, evidence for their efficacy is limited. Given the lack of level 1 evidence and a previously inconclusive Cochrane review, this study aimed to determine whether prednisolone or aciclovir used early in the course of Bell's palsy could improve the chances of recovery.

Methods

Patients: 551 patients at 17 centres in Scotland.

Inclusion criteria:

- Age >16y;
- Unilateral facial nerve weakness of no identifiable cause;
- Presenting to 1° care or ED with referral for otorhinolaryngology opinion within 72h of onset.

Exclusion criteria:

- Pregnant or breastfeeding;
- Medical: uncontrolled DM, peptic ulcer disease, sarcoid;
- Infections: systemic, herpes zoster virus (HZV), middle ear infection.

Groups: Randomized twice to give four groups (2×2 factorial design):

- Prednisolone (25mg bd) and aciclovir (400mg 5 \times /d) for 10d ($n = 134$);
- Placebo (lactose) and aciclovir ($n = 138$);
- Prednisolone and placebo ($n = 138$);
- Placebo and placebo ($n = 41$).

Primary outcome: House–Brackmann grading system for facial nerve function (score 1–6, with 1 = normal function). Function independently graded using photographs and blinded to study group assignments. The primary outcome was full recovery with a final score of 1.

Follow-up: Baseline visit at home/doctor's office at 3–5d, then at 3mo. If recovery incomplete, visit at 9mo performed.

Results

Table 14.17 Summary of results

| Full recovery | Pred | No pred | <i>p</i> | Aciclovir | No aciclovir | <i>p</i> |
|---------------|--------------------|--------------------|----------|--------------------|--------------------|----------|
| At 3mo | 205/247 (83%) | 152/239 (63.6%) | <0.001 | 173/243 (71.2%) | 184/243 (75.7%) | 0.5 |
| At 9mo | 237/251 (94.4%) | 200/245 (81.6%) | <0.001 | 211/247 (85.4) | 226/249 (90.8%) | 0.1 |

Sample size calculation showed 236 per treatment, at 80% power, 0.05 significance level, to demonstrate a 10–12% difference in treatments.

Discussion

This study represents the strongest evidence available in answering how best to treat Bell's palsy. The fact that a previous Cochrane review was inconclusive did not mean there was 'no evidence', just that there was a lack of well-powered level 1 trials. That said, there has been weaker evidence also recommending aciclovir in Bell's palsy. In this RCT, aciclovir did not offer any benefit. A recent Japanese RCT (Hato *et al. Otol Neurotol* (2007) 23, 408–13) recommended the use of valaciclovir in the treatment of Bell's palsy, but only for those patients with complete facial palsy. However, the study was not powered for subgroup analysis, and facial function was not independently graded. (See Table 14.17.)

Some may argue the ethics of offering placebo to patients in this trial, given that the majority of specialists had already advocated the use of steroids. However, further placebo-controlled treatment trials of Bell's palsy were published around the same time or later, indicating that considerable uncertainty existed, and placebo-controlled treatment was regarded as ethical to be able to create definitive evidence. More recently, though, the comparison group in such trials has been treatment with steroids, usually compared to additional antiviral medication.

Psychiatry

- Introduction 388
- Depression: antidepressants 390
- Depression: relapse prevention 392
- Depression: electroconvulsive therapy 394
- Depression: collaborative care 396
- Bipolar disorder: discontinuation of lithium therapy 398
- Schizophrenia: atypical vs typical antipsychotics 400
- Schizophrenia: relapse prevention 402
- Schizophrenia: management of treatment-resistant disease 404
- Panic disorder: cognitive therapy 406
- Panic disorder: pharmacological and psychological treatment 408
- Bulimia nervosa: cognitive vs standard behavioural therapy 410
- Eating disorders (anorexia and bulimia nervosa): family therapy 412
- Attention-deficit/hyperactivity disorder: medication 414
- Chronic fatigue syndrome: non-pharmacological treatments 416

Introduction

The psychiatrist at the cinema: The popular image of psychiatry is not great, and unhelped by films such as *'One Flew Over the Cuckoo's Nest'* (starring Jack Nicholson), *'Girl: Interrupted'* (Winona Ryder, Angelina Jolie), and *'A Beautiful Mind'* (Russell Crowe). But there are strongly positive models too, such as that of William Rivers in *'Regeneration'* (Jonathan Pryce), of Oliver Sacks in *'Awakenings'* (Robin Williams), and of the fictional Dr Powell in *'K-Pax'* (Jeff Bridges, Kevin Spacey). One of *K-Pax's* themes, the toll on psychiatrists of their work, is the focus of *'Face to Face'*, which makes for challenging viewing, as Liv Ullman portrays a fictional psychiatrist who inexorably declines with her own mental illness. If after watching that you need a pick-me-up (and you will), *'High Anxiety'* should help, as Mel Brooks plays the fictional Dr Thorndyke, a medical superintendent at the 'Psychoneurotic Institute for the Very, VERY Nervous'.

The psychiatrist at parties: Responding to the party question 'what do you do?' is challenging for any doctor, but, for a psychiatrist, it is particularly problematic. There are three likely responses to 'I'm a psychiatrist, actually' (the 'actually' immediately betraying nervousness about revealing this information). Some people are firmly dismissive, appearing to believe that the psychiatrist is expressing grandiose delusions and is actually in need of psychiatric help himself or herself. Many will latch onto the poor psychiatrist for the rest of the night, sharing their neuroses and seeking advice, such that the party becomes an extension of the outpatient clinic. And others appear disconcerted—'oh, you've been analysing me, haven't you, why didn't you tell me that earlier?'. While the narcissistic among psychiatrists will relish these responses, most psychiatrists have unsurprisingly learnt the hard way to keep their occupation close to their chests, and some have developed elaborate alter egos in order to cope. Now, what did you say that you do...?

Depression: antidepressants

Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability.

AUTHORS: Anderson IM.

REFERENCE: *J Affect Disord* (2000) **58**, 19–36.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Selective serotonin reuptake inhibitors (SSRIs) are better tolerated than TCAs with comparable efficacy.

Impact

Since this systematic review, TCAs have been replaced by SSRIs as first-choice antidepressant agents.

Aims

SSRIs had become increasingly popular for the treatment of depression, due to reportedly better SE profiles and safety than TCAs. This study aimed to compare their efficacy and tolerability.

Methods

Patients: 102 RCTs (10,706 participants) included.

Inclusion criteria:

- RCTs;
- Unipolar major depressive illness;
- SSRI vs TCA (including the tetracyclic agent maprotiline).

Search strategy:

- Previous meta-analyses and reviews;
- Medline search (to May 1997).

Outcomes:

- Reduction in scores on Hamilton Rating Scale for Depression (HAM-D) or Montgomery and Asberg Depression Rating Scale (MADRS);
- Treatment discontinuation: overall/due to SEs.

Results

- Efficacy:
 - Overall, SSRIs and TCAs were of equal efficacy (effect size -0.03 , 95% CI -0.09 to 0.03);
 - In a subgroup analysis, it appeared TCAs were more effective than SSRIs in the treatment of depressed inpatients, i.e. patients with severe depression (effect size -0.23 , 95% CI -0.4 to -0.05 ; 25 trials, 1,377 participants);
- SEs:
 - More people discontinued TCAs due to SEs than SSRIs (17.3% vs 12.4%, $p < 0.0001$).

Discussion

The SSRIs have largely replaced TCAs as first-line agents for unipolar depression. This analysis provided a rational basis for this change in prescribing; the SSRIs were generally as effective and better tolerated.

Problems

- Subgroup analyses: Multiple subgroup analyses were performed, which may have increased the risk of finding erroneous differences.
- Newer antidepressants: The analysis did not address newer antidepressant agents such as the selective serotonin/norepinephrine reuptake inhibitors (SNRIs), venlafaxine, and duloxetine. Superior efficacy is claimed for some of these agents.
- Age: This evidence applies only to adults; there is active debate regarding the effectiveness and risks of antidepressants (SSRIs in particular) in children and adolescents.
- Risk of deliberate self-harm/suicide: There is an active debate regarding the risk of suicide, following antidepressant prescription. Clearly, this is challenging epidemiology; depression is associated with both suicide and antidepressant prescription, and the emergence of suicidal ideation may trigger pharmacological treatment.

Depression: relapse prevention

Relapse prevention with antidepressant drug treatment in depressive disorders.

AUTHORS: Geddes J, Carney S, Davies C *et al.*

REFERENCE: *Lancet* (2003) **361**, 653–61.

STUDY DESIGN: Meta-analysis (systematic review)

EVIDENCE LEVEL: 1a

Key message

Antidepressant continuation substantially reduces the risk of relapse in depressive disorder.

Impact

The relapse prevention benefits of treatment underlie the standard recommendation to continue antidepressants for 6mo or more after recovery. Much more effort is now placed on educating patients about the likely benefits of continuing treatment with antidepressants beyond the point of recovery.

Aims

As depression often has a long-term course, patients remain at risk of relapse after successful treatment of acute episodes. Therefore, guidelines often recommend continuation of treatment for several months after recovery. However, there had been no consensus in practice. This review aimed to establish how long antidepressants should be continued to prevent relapse in depression.

Methods

Inclusion criteria:

- Study type: RCTs;
- Publication status: Published or unpublished, available at August 2000;
- Comparison: Continued antidepressant vs placebo;
- Participants: Already responded to acute antidepressant treatment.

Groups:

- Continued antidepressant;
- Placebo.

Search strategy:

- A Cochrane Collaboration Trials Register, which incorporated searches of Medline, EMBASE, Cinahl, PsycLIT, Psynindex, and Lilacs;
- Reference checking;
- Personal communications.

Outcome: Relapse or recurrence of depression.

Results

- Thirty-one trials (4,410 participants) provided data for analyses;
- Trials compared placebo with most classes of antidepressant, although the majority involved a TCA or an SSRI.
- Continued antidepressant treatment reduced the risk of relapse by roughly half (41% vs 19%, pooled OR 0.30, 95% CI 0.22–0.38). This reduction was similar for the antidepressant classes for which there was most evidence (15 TCA trials, ten SSRI trials), and was also independent of treatment duration.

Discussion

This meta-analysis demonstrated the benefits of continuing antidepressant medication after recovery from an episode of depression. The large body of data and consistency of the findings allow for considerable confidence in interpretation. Most of the trials were of 12mo duration, although consistent benefits were seen, even in those that extended to 3y F/U. The magnitude of effect was so great to support speculation that antidepressant medications are actually more effective at relapse prevention than promoting initial recovery.

Problems

- Lack of individual patient data analysis: The analyses were performed on the overall results of studies. Availability of individual patient data might have allowed identification of subgroups receiving different magnitudes of benefit.
- Applicability in 1° care: The trials mainly recruited patients from 2° care. It is possible (although unproven) that the benefits may not apply to 1° care populations with a lower baseline risk of relapse.
- Duration of protective effects: From 3y onwards, the problem becomes a lack of evidence for efficacy, rather than evidence of lack of efficacy. Given that antidepressants are often taken for several years, further studies extending the evidence over longer time periods would be of benefit.

Depression: electroconvulsive therapy

The Northwick Park electroconvulsive therapy Trial

AUTHORS: Johnstone E, Deakin J, Lawler P *et al.*

REFERENCE: *Lancet* (1980) 2, 1317–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Electroconvulsive therapy (ECT) is superior to sham therapy for acute depression. However, results are not sustained at long-term F/U.

Impact

ECT remains the most controversial standard psychiatric treatment. Despite vehement opposition of some patients and patient groups, ECT remains a recommended treatment option for some people with severe depression. Indeed, in certain clinical situations, ECT remains an essential lifesaving treatment.

Aims

ECT was first introduced over 40y prior to this study. Its use had always been shrouded in controversy, not helped by a limited evidence base. With only a limited number of small studies, there was uncertainty whether the electric shock was the essential therapeutic element or whether the anaesthetic itself might act as an antidepressant. Therefore, this study aimed to determine whether the electric shock, and the resulting convulsion, is a required element.

Methods

Patients: 70 patients (52 ♀, 18 ♂) from one centre in the UK.

Inclusion criteria:

- Endogenous depression;
- Considered probable good response to ECT;
- Age 30–69y;
- Admitted to hospital for treatment and consent to ECT.

Groups:

- Real ECT (up to eight treatments over 4wk);
- Sham ECT (anaesthesia without ECT).

Primary endpoint: Improvement in depressive symptoms (Hamilton rating scale).

Secondary endpoints:

- Other rating scales for depression severity;
- Tests of memory and concentration.

Follow-up: Weekly during study, and subsequently at 1 and 6mo after completion.

Results

- Greater initial improvement in depression ratings was seen with real ECT than with sham treatment ($p < 0.01$);
- The comparative benefit was no longer evident at 1 or 6mo F/U;
- Real ECT was associated with subjective and objective memory deficits during the course of treatment, but there was no evidence of sustained problems.

Discussion

This study showed that ECT is more effective than sham therapy for patients with severe depression, leading to rapid resolution of the severe depressive state. The difference between groups was smaller than the substantial improvement in both over the course of the study. The specific benefits of ECT over anaesthesia alone seen during treatment were not convincingly sustained in the longer term.

Problems

- Cognitive SEs: While this study did not find evidence of prolonged memory impairments after treatment, the tests used may not have been optimal. Tests of cognitive function have tended to be inconsistent between studies of ECT.
- Patient and carer attitudes: Acceptance of the need for this treatment is often low among patients and carers, perhaps fuelled by legitimate concerns about possible adverse effects (including cognitive SEs) and by potent media influences (such as alarming images seen in films like *'One Flew Over the Cuckoo's Nest'* starring Jack Nicholson).
- Consent to treatment: Many patients who fulfil criteria for ECT lack the capacity to consent to treatment.

Depression: collaborative care

PROSPECT (Prevention of Suicide in Primary Care Elderly: Collaborative Trial): Long term effect of depression care management on mortality in older adults: follow-up of cluster randomized clinical trial in primary care.

AUTHORS: Gallo JJ, Morales KH, Bogner HR et al.

REFERENCE: *BMJ* (2013) 346, f2570.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Multifaceted collaborative care significantly improves mortality in the treatment of major depression.

Impact

PROSPECT is the latest in a series of trials of 'collaborative care', originating with Katon's pivotal 1995 *JAMA* study, which demonstrate improved depression outcomes. The group are also contributing to an emerging evidence base that depression significantly worsens physical health outcomes and that effective depression management can significantly improve physical health outcomes.

Aims

Until recently, the focus of treatment for depression was almost entirely based on which treatment or treatments should be delivered—an antidepressant, and, if so, which one and for how long; or, if not, a psychological treatment, which one, and for how long. This Seattle group's ongoing work on 'collaborative care' has shifted attention towards the broad context of treatment delivery, supporting explanation by clinician, video, or booklet, education of professionals, structured F/U, and monitoring of adherence, to name but a few. This study aimed to compare the effectiveness of multifaceted collaborative care with usual care in reducing mortality in patients with mild to moderate depression in a 1° care setting in the USA.

Methods

Participants: 599 patients from 20 1° care clinics in the USA.

Inclusion criteria:

- Centre for Epidemiological Studies Depression Scale (CES-D) score >20;
- Age ≥60y;
- MMSE >17;
- Separate analysis for major depression and minor depression by Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. A further group ($n = 627$) without depression also followed up.

Interventions:

- Collaborative care: Depression care manager worked within practice to recommend treatment, according to PROSPECT guidelines, and monitored symptoms, adverse effects, and adherence to treatment; education for physicians and for families ($n = 320$);
- Usual care: practices received educational sessions for physicians and notification of depression status of patients ($n = 279$).

Endpoint: Death.

Follow-up: Median 98mo (range 0.8–116.4). This is a longer-term F/U after an initial RCT (PROSPECT) of 12mo duration.

Results

- Patients with major depression: Intervention associated with lower risk of death than usual care (HR 0.76; 95% CI 0.57–1.00);
- Patients with minor depression: No significant difference in risk of death between conditions (HR 1.18; 95% CI 0.77–1.81)

Discussion

The multifaceted approach to intervention led to reduced mortality in patients with major depression during average F/U of over 8y. It is notable that, while the study was originally designed to assess prevention of suicide, the effect seen was on all-cause mortality, particularly physical causes. This finding in 1° care is concordant with an emerging evidence base that depression significantly worsens physical health outcomes and that effective depression management can significantly improve physical outcomes.

Problems

- Using the correct recipe: It is unclear which aspects of collaborative care were the effective ingredients; were all aspects essential or only some? Was the effect of the whole greater than that of the sum of the parts through synergistic effects, and, if so, how could this be determined?
- Applicability: This study was conducted in the US health-care system, and it is likely that the effectiveness or otherwise of 'health-care system' interventions is nation- and system-specific. However, there is growing evidence of the global effectiveness of such interventions.

Further reading

- Bruce M, Ten Have TR, Reynolds CF 3rd et al. (2004). Reducing suicidal ideation and depressive symptoms in depressed older primary care patients: a randomized controlled trial. *JAMA* 291, 1081–91 (the report of 12mo F/U of the PROSPECT study).
- Katon W, Von Korff M, Lin E et al. (1995). Collaborative management to achieve treatment guidelines. Impact on depression in primary care. *JAMA* 273, 1026–31 (the first trial of collaborative care).

Bipolar disorder: discontinuation of lithium therapy

Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders.

AUTHORS: Faedda G, Tondo L, Baldessarini R *et al.*

REFERENCE: *Arch Gen Psychiatry* (1993) 50, 448–55.

STUDY DESIGN: Cohort.

EVIDENCE LEVEL: 2a.

Key message

Gradual discontinuation of lithium is less likely to lead to early relapse than rapid discontinuation.

Impact

The need for gradual discontinuation is a key component of the effective and safe prescription of lithium. Patients need to be fully informed about the medicine, and how to maximize its effectiveness and minimize its SEs.

Aims

Long-term maintenance therapy with lithium is a common approach in the management of bipolar disorder. However, although there is now reasonable support for its effectiveness, there is relatively little evidence guiding its use. Patients stop their medicines for a variety of reasons, with or without the endorsement of their doctor. In chronic disorders, such as bipolar disorder, withdrawal of prophylactic treatment may be especially likely after a period of stability. At the time of this study, it was not known what advice regarding the speed of withdrawal should be given to such patients.

Methods

Patients: 64 patients from one psychiatry outpatient clinic in Italy.

Inclusion criteria:

- DSM-III-R bipolar disorder;
- Stable on lithium monotherapy for ≥ 18 mo;
- Stopped lithium for reason other than recurrence.

Groups:

- Gradual discontinuation (2–4wk) ($n = 30$);
- Rapid discontinuation (< 2 wk) ($n = 34$).

Primary endpoint: Relapse to episodes of mania or depression.

Follow-up: 5y.

Results

Table 15.1 Summary of results

| Endpoint | Gradual discontinuation | Rapid discontinuation | <i>p</i> |
|---------------------------|-------------------------|-----------------------|----------|
| Recurrent episode | 16/30 (53%) | 32/34 (94%) | <0.001 |
| Median time to recurrence | 37mo | 8mo | <0.001 |

Discussion

The excess of recurrent episodes of mood disorder was most apparent in the early months after discontinuation. After 2y, it was the same in both groups. The increased rate of relapse on rapid discontinuation was so great that prolonged treatment over several years was necessary for the benefit accrued by taking lithium to outweigh the harm caused by rapid discontinuation. The results of this study raised the concern that rapid discontinuation of lithium in patients with (apparently) unipolar mood disorder may trigger an episode of hypomania or mania, and thereby a change of diagnosis to bipolar disorder. (See Table 15.1.)

Problems

- Study design: This was an observational study, and not a randomized trial. Therefore, patient characteristics may have affected speed of discontinuation, biasing the results.
- Differences between study groups: Gender, age, and mean duration of lithium treatment were similar in the two groups. However, bipolar patients were commoner in the rapid withdrawal group and more likely to relapse earlier.
- Unplanned discontinuations: Compliance with prescribed medication is often poor, so discontinuations are unplanned and sudden. Patient education is pivotal.

Further reading

These two important studies below (RCT and systematic review, respectively) have added to the evidence base for the use of lithium in the long-term management of bipolar disorder.

BALANCE investigators and collaborators, Geddes JR, Goodwin GM, Rendell J *et al.* (2010). Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* **375**, 385–95.

Cipriani A, Hawton K, Stockton S, Geddes J (2013). Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis. *BMJ* **346**, f3646.

Schizophrenia: atypical vs typical antipsychotics

CATIE (**C**linical **A**ntipsychotic **T**rials of **I**ntervention **E**ffectiveness) study: Effectiveness of antipsychotic drugs in patients with chronic schizophrenia.

AUTHORS: Lieberman JA, Stroup TS, McEvoy JP et al.

REFERENCE: *N Engl J Med* (2005) **353**, 1209–23.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Typical and atypical antipsychotics have similar efficacy in schizophrenia.

Impact

Atypical antipsychotics took psychiatric practice by storm in the late 1990s and, by 2000, were the dominant prescription in developed nations. This trial (and other evidence of adverse effects) is encouraging a return to older typical antipsychotic medications as options in the treatment of psychosis.

Aims

The first generation of antipsychotic drugs (dopamine D2 receptor agonists) had high rates of neurological SEs, including extrapyramidal signs and tardive dyskinesia. Second-generation (atypical) agents have lower affinity for D2 receptors and higher affinity for other receptors, including those for 5-hydroxytryptamine (serotonin) and norepinephrine. Although these increasingly popular agents had been proposed to have fewer SEs, there was no firm evidence as to their efficacy. Therefore, this study aimed to compare the effectiveness of atypical and conventional antipsychotic medications in schizophrenia.

Methods

Patients: 1,460 patients from 57 clinical sites in the USA.

Inclusion criteria:

- Age 18–65y;
- Schizophrenia: DSM-IV criteria.

Groups:

- Four 'atypical' groups: olanzapine ($n = 336$), quetiapine ($n = 337$), risperidone ($n = 341$), ziprasidone ($n = 185$);
- One 'typical' group: perphenazine (an older 'typical' or 'conventional' agent that was not well known to clinical investigators ($n = 261$)).

Primary outcome: Discontinuation of treatment (any cause).

Secondary outcomes:

- Reason for discontinuation;
- Rating scale scores (Clinical Global Impression (CGI) and Positive and Negative Syndrome Scale (PANSS));
- Measures of safety and tolerability.

Follow-up: 18mo.

Results

- The majority (74%) of patients discontinued their assigned medication over the course of the 18mo study;
- Olanzapine was the agent least likely to be discontinued for any reason (HR 80.7 vs other agents). It was also least likely to be discontinued, because of lack of efficacy (HR 80.45);
- The conventional and atypical agents had similar efficacy on the rating scale measures and on ratings of motor SEs;
- Olanzapine use was associated with a greater increase in weight, total cholesterol, triglycerides, and HbA_{1c} than the other agents.

Discussion

The newer 'atypical' antipsychotics are now widely prescribed, following the perception that they are both more effective and have fewer SEs than the older 'conventional' or 'typical' antipsychotics. Both these beliefs had come under question in the period leading up to this study. A meta-analysis had found that the newer and older agents were, in fact, of similar short-term efficacy and tolerability (see Geddes *et al. BMJ* (2000) 321, 1371–6), and there had been increasing awareness of the specific SE profiles of the atypicals. This well-powered study found that the typical antipsychotic perphenazine was not inferior to most of the atypical agents. Similar findings of equivalence between the classes have more recently come from the UK CUTLASS 1 study (*Arch Gen Psych* (2006) 63, 1079–87). This study further suggests that there may be some specific benefit of olanzapine over other antipsychotics assessed, but at the cost of increased risk of metabolic SEs.

Problems

- Meaning of discontinuation: The primary outcome of discontinuation of treatment could be due to many causes, not simply differences in efficacy.
- Choice of typical antipsychotic: Perphenazine had not been widely used previously.
- Dose equivalence: The effective olanzapine dosage achieved in the study may have been higher than for comparator agents, contributing to apparent differences in effects.

Schizophrenia: relapse prevention

Continuous versus targeted medication in schizophrenic outpatients: outcome results.

AUTHORS: Carpenter W, Hanlon T, Heinrichs D *et al.*

REFERENCE: *Am J Psychiatry* (1990) 147, 1138–48.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Continuous antipsychotic medication is more effective at preventing relapse in schizophrenia than intermittent use.

Impact

Continued antipsychotic medication is a key component of schizophrenia management. Therefore, a key function of community mental health teams is increasing patient adherence to antipsychotic medication. Indeed, a psychological treatment ('compliance therapy') has been developed with this aim in mind, although evaluation of its effectiveness has been limited to date.

Aims

Schizophrenia is a common mental disorder, which can have a major and enduring impact on functional capacity. Antipsychotic medication has improved outcomes but is associated with adverse effects in the short term and potentially the long term (tardive dyskinesia). This trial aimed to compare the effects of continued or intermittent antipsychotic use as a component of outpatient schizophrenia management.

Methods

Patients: 116 outpatients at one centre in the USA.

Inclusion criteria:

- Schizophrenia;
- Recent psychotic episode;
- Considered appropriate for long-term antipsychotic therapy.

Groups: Both groups received 'enriched psychosocial care', including weekly individual therapy:

- Continuous medication ($n = 59$);
- Intermittent medication (drug-free, unless symptomatic) ($n = 57$).

Key outcomes:

- Admission to hospital;
- 'Decompensation' (worsening of functioning or symptoms);
- Total medication required.

Follow-up: 2y.

Results

Table 15.2 Summary of results

| Endpoint | Continuous | Intermittent | <i>p</i> |
|------------------------------------|------------|--------------|----------|
| Admissions | 36 | 60 | <0.05 |
| Decompensations (mean per patient) | 2.75 | 4.21 | <0.05 |

Discussion

Antipsychotic medications are not without SEs, so reducing their use is potentially desirable. This research group had previously found that intermittent medication, in combination with enriched psychosocial care, had been equivalent to care as usual. In this study, both groups received psychological intervention, so any differences should reflect the choice of medication strategy. While intermittent medication targeted to early signs of relapse did reduce the dose of antipsychotic received, it was at the cost of a worse clinical outcome with more recurrent episodes of illness. This was demonstrated not only in the number of 'decompensations' recorded by treating clinicians, but also in terms of the hard endpoint of need for hospital admission. (See Table 15.2.)

Problems

- Decision-making for individuals, not populations: Schizophrenia is a highly varied disease, and one approach may not fit all patients. While intermittent antipsychotic medication may increase the risk of relapse, there may be patients for whom the reduction in dose, and presumably SEs, makes that a reasonable trade-off.
- Possibility of increased risks, as well as reduced benefits: tardive dyskinesia is a chronic, irreversible neurological disorder associated with the prescription of antipsychotics. There has been some concern that it may be more likely when antipsychotics are prescribed intermittently.

Schizophrenia: management of treatment-resistant disease

Clozapine for the treatment-resistant schizophrenic.

AUTHORS: Kane J, Honigfeld G, Singer J, Meltzer H.

REFERENCE: *Arch Gen Psychiatry* (1988) 45, 789–96.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Clozapine is more effective than alternative antipsychotics in treatment-resistant schizophrenia.

Impact

This trial led to the reintroduction of clozapine into psychiatric practice. Clozapine is now the antipsychotic of choice in treatment-resistant schizophrenia (defined as a lack of response, following the sequential use of the recommended doses for 6–8wk of at least two antipsychotics, at least one of which should be an ‘atypical’). Mandatory blood monitoring is required, in view of the small risk of agranulocytosis.

Aims

A number of studies had identified subgroups of patients who failed to respond to neuroleptic drug therapy, including a group that relapse despite initial successful therapy. Previous studies had reported efficacy in these patients from the atypical agent clozapine, showing this to be superior to the dopamine receptor antagonist chlorpromazine. Despite this, its use had been withdrawn, due to case reports of agranulocytosis. This study aimed to evaluate the efficacy of clozapine in the treatment of schizophrenia that had already failed to respond to other antipsychotic agents.

Methods

Patients: 268 inpatients from 16 treatment centres in the USA.

Inclusion criteria:

- Schizophrenia: DSM-III criteria;
- Failure to respond to at least three different antipsychotics.

Groups:

- Clozapine ($n = 126$);
- Chlorpromazine and benztropine ($n = 139$).

Primary outcome: Improvement on CGI and Brief Psychiatric Rating Scale (BPRS).

Secondary outcomes:

- Clinically significant improvement: Defined as >20% reduction in BPRS score, and either CGI rating as 'mild' or better, or BPRS score <36;
- Nurses' Observation Scale for Inpatient Evaluation (NOSIE-30);
- Assessment of adverse reactions and safety.

Follow-up: At 6wk.

Results

- Patients receiving clozapine showed greater improvement than those receiving chlorpromazine. This was evident on both the CGI ($p < 0.001$) and BPRS ($p < 0.001$).
- 30% of those receiving clozapine 'improved' to an extent that was clinically significant, compared to only 4% of those receiving chlorpromazine ($p < 0.001$).
- Statistical superiority for clozapine was also seen for subscales of the BPRS (positive, negative, and general symptoms) and on the nurse-rated NOSIE.

Discussion

While many patients with schizophrenia receiving an antipsychotic agent experience benefit, failure to respond remains a major clinical problem. Use of clozapine was associated with particular risks (notably the increased rates of agranulocytosis), but this study established its particular place in the treatment of those who fail to respond to other antipsychotic medication.

Problems

- Uncertainty about pharmacological action: The pharmacological basis of the superiority of clozapine remains unclear. Attempts to develop molecules with similar efficacy, but without serious SEs, have as yet been unsuccessful.
- Dose titration: Due to SEs, clozapine requires careful dose titration in the first month and daily dosing without breaks. Alongside the need for careful blood monitoring, this means that patient cooperation is essential.
- Extent and duration of response: Only 30% of participants receiving clozapine experienced clinically significant improvement at short-term F/U; this trial did not tell us whether clozapine was more or less effective over longer periods of time that would have greater clinical relevance.

Panic disorder: cognitive therapy

A crossover study of focused cognitive therapy for panic disorder.

AUTHORS: Beck A, Sokol L, Clark D *et al.*

REFERENCE: *Am J Psychiatry* (1992) **149**, 778–83.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Cognitive therapy (CT) is an effective non-pharmacological treatment for panic disorder.

Impact

This trial was one of the first to demonstrate the effectiveness of CT for a common psychiatric disorder. The results have been reproduced several times, contributing to the emergence of CT (and the very closely related cognitive behavioural therapy, CBT) as the dominant psychotherapy with a strong and developing evidence base. Therefore, both pharmacological and non-pharmacological options are available for several common psychiatric disorders, including panic. Patients can be asked which approach they prefer.

Aims

In 1992, common pharmacological treatments for panic disorder included benzodiazepines and the TCA imipramine, both of which had significant adverse effects. Behavioural approaches and combined cognitive and behavioural approaches had started to emerge but had not been rigorously evaluated in a randomized trial. This RCT aimed to compare the effectiveness of CT with that of brief supportive psychotherapy (SP) in outpatients with panic disorder.

Methods

Patients: 33 patients at one outpatient clinic in the USA.

Inclusion criteria:

- Meeting DSM-III diagnostic criteria for panic disorder or agoraphobia with panic attacks;
- Age 18–65y.

Groups:

- CT: 12-weekly individual sessions with a trained cognitive therapist ($n = 17$);
- SP: 8-weekly individual sessions of supportive contact with a trained therapist, based on client-centred therapy principles ($n = 16$).

Primary endpoint: Clinician rating of absence of weekly panic attacks at 8wk.

Secondary endpoints:

- Self-rating of panic frequency at 8wk;
- Self-rating of panic intensity at 8wk;
- Beck Anxiety Inventory (BAI) score;
- Beck Depression Inventory (BDI) score.

Follow-up: Before treatment, then at 4 and 8wk.

Results

Table 15.3 Summary of results

| Primary endpoint | CT | SP | <i>p</i> |
|---------------------------------------|---|-----------|----------|
| No weekly panic attacks, <i>n</i> (%) | 12 (71%) | 4 (25%) | <0.02 |
| Secondary endpoints | (group by time interaction, linear trend) | | |
| Panic frequency, mean (SD) | 0.4 (0.6) | 3.1 (4.1) | <0.01 |
| Panic intensity, mean (SD) | 1.2 (1.8) | 2.5 (1.5) | <0.01 |
| BAI score, mean (SD) | 15 (13) | 27 (14) | <0.03 |
| BDI score, mean (SD) | 7 (6) | 14 (11) | <0.03 |

Discussion

These results provided convincing evidence of the short-term effectiveness of CT, compared to a control intervention that was not expected to be effective. (See Table 15.3.)

Problems

- **Long-term data:** Unfortunately, in this trial, SP participants were able to choose to cross-over to CT at 8wk, and all chose to do so. Therefore, long-term comparative data are unavailable from this trial.
- **Cost:** 12 sessions of individual therapy would be considered labour-intensive and expensive for such a common disorder. Group CT, computerized CT, and self-help CT via books or the Internet offer ways of reducing therapist time and expense.
- **Availability:** CT is a specialized treatment; in the UK, there is a shortage of staff appropriately trained to deliver it.
- **Applicability:** This trial was conducted at an innovative 'Centre for Cognitive Therapy', and there is evidence that treatment effects at such centres are greater than in 'ordinary' health service settings.

Panic disorder: pharmacological and psychological treatment

Paroxetine in the treatment of panic disorder.

AUTHORS: Oehrberg S, Christiansen P, Behnke K et al.

REFERENCE: *Br J Psychiatry* (1995) **167**, 374–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The combination of an SSRI antidepressant and CT for the treatment of panic disorder is more effective than CT alone.

Impact

Combination therapy is now widely used for panic disorder. However, due to the limited availability of formal individual CT, the usual psychological approach is an SSRI, combined with cognitively informed self-help using written materials or computerized CBT.

Aims

Both pharmacological and psychological treatments had been shown to have efficacy in the treatment of panic disorder. Drug treatments had centred on higher-dose benzodiazepines; however, adverse effects led to increased study of antidepressants, particularly SSRIs. While these had been demonstrated to be successful, their use had not been compared to the mainstay of psychological therapy CT. This study aimed to evaluate the efficacy and tolerability of combined paroxetine (SSRI) and CT vs CT alone in the treatment of panic disorder.

Methods

Patients: 120 patients from multiple Danish centres.

Inclusion criteria:

- DSM-III-R panic disorder;
- Age 18–70y;
- No significant depression (Hamilton Depression Scale ≤ 14);
- No psychosis, organic brain disease, alcohol, or drug misuse.

Groups:

- CT and SSRI (paroxetine): Dose titrated to low (20mg/d), or medium (40mg/d), or high (60mg/d) ($n = 60$);
- CT and placebo ($n = 60$).

Primary outcome: Frequency of panic attacks in 3wk periods.

Secondary outcomes:

- 50% reduction in Hamilton Anxiety Scale score (Ham-A);
- CGI mildly ill or better;
- Mean reduction on Zung Self-Rating Scale for Anxiety.

Follow-up: At 3, 6, 9, and 12wk.

Results

Table 15.4 Summary of results

| Outcome (at 12wk) | CT and SSRI | CT and placebo | RR (95% CI) |
|--------------------------------|-------------|----------------|------------------|
| Primary outcomes | | | |
| 50% decrease in panic attacks | 42/60 | 25/60 | 1.68 (1.19–2.37) |
| 0 or 1 panic attack in 3wk | 19/60 | 8/60 | 2.38 (1.13–5.0) |
| Secondary outcomes | | | p |
| 50% reduction in Ham-A | 85% | 51% | <0.001 |
| CGI mildly ill or better | 71% | 40% | 0.003 |
| Zung mean change from baseline | –6.5 | –4.3 | 0.04 |

Discussion

This trial demonstrated a clear benefit for the combination of SSRI and CT over CT alone. While other RCTs have not typically found such a striking magnitude of benefit, it has been shown overall that a combination of medication and psychological therapy is superior to either alone (e.g. see Furukawa *et al. Br J Psychiatry* (2006), 188, 305–12). (See Table 15.4.)

Problems

- **Duration of effect:** The duration of the study was only 12wk, and it is uncertain whether differences would persist over the longer term. There is some evidence that the benefits of combination therapy over psychological interventions alone tend to be lost, as medication is discontinued.
- **Attitudes to treatment:** Some patients are ambivalent or against taking medication, and especially reluctant to take ‘antidepressants’ when they are not depressed.
- **Applicability:** Many patients presenting with panic disorder have some depressive symptoms or will be misusing alcohol or street drugs. Application of the findings to these patients is uncertain.

Bulimia nervosa: cognitive vs standard behavioural therapy

Three psychological treatments for bulimia nervosa. A comparative trial.

AUTHORS: Fairburn C, Jones R, Peveler R et al.

REFERENCE: *Arch Gen Psychiatry* (1991) **48**, 463–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

CBT is an effective psychological treatment for bulimia nervosa.

Impact

In the late 1980s, eating disorders were emerging as a major clinical problem, yet there was a dearth of evidence regarding the effectiveness of treatment. Cognitive interventions were just starting to be developed and assessed. This trial demonstrated the value of CBT above that of the simpler psychological treatment behaviour therapy (BT). CBT has been endorsed in the UK as the preferred psychological treatment for patients with bulimia nervosa.

Aims

Both pharmacological and psychological treatments have been considered for bulimia nervosa. Most research into psychological therapies had focused on CBT, though many studies had found no differences in outcomes between this and other psychological therapies. This study aimed to determine whether: (a) CBT was more effective than control psychotherapy (interpersonal psychotherapy, IPT) and (b) the simpler BT was as effective as CBT.

Methods

Patients: 75 patients from multiple 1° and 2° care centres in the UK.

Inclusion criteria: Bulimia nervosa by DSM-III-R criteria:

- Age ≥ 17 y;
- BMI $> 17 \text{ kg/m}^2$.

Groups: Each intervention comprised outpatient psychotherapy (19 sessions over 18wk):

- CBT: combination of behavioural (eating normalization) and cognitive (focus on patient's concerns regarding their shape and weight) ($n = 25$);
- BT: focus only on normalization of eating ($n = 25$);
- IPT: modified for bulimia nervosa ($n = 25$).

Endpoints: No primary endpoint was specified:

- Frequency of core symptoms, per 28d, including objective binge-eating episodes, self-induced vomiting, and laxative misuse;

- Eating Disorders Examination (EDE) subscales, including dietary restraint, attitudes to shape, and attitudes to weight;
- Eating Attitudes Test (EAT) score;
- Psychiatric symptoms, including the BDI.

Follow-up: Before start of treatment and at end of treatment.

Results

Table 15.5 Summary of results

| Endpoint (means, at treatment end) | CBT | BT | IPT | <i>p</i> (3-way) | <i>p</i> ≤0.05 (2-way) |
|------------------------------------|------|------|------|------------------|------------------------|
| Binge frequency | 0.6 | 1.3 | 1.8 | 0.4 | |
| Vomiting frequency | 1.5 | 0.9 | 5.5 | 0.03 | CBT > IPT |
| EDE restraint | 1.3 | 2.3 | 2.1 | 0.05 | CBT > IPT; CBT > BT |
| EDE shape | 2.1 | 3.3 | 2.6 | 0.01 | CBT > BT |
| EDE weight | 1.7 | 2.9 | 2.4 | 0.01 | CBT > IPT; CBT > BT |
| BDI | 10.1 | 13.6 | 12.5 | 0.5 | |

Discussion

All three treatments helped; they were each associated with significant reductions in binge frequency. However, there were some notable differences in effectiveness. For example, the frequency of vomiting was reduced by both CBT and BT, but not by IPT; and CBT was more effective on all the core endpoints, including measures of dietary restraint and attitudes to shape and weight. (See Table 15.5.)

Problems

- **Applicability:** The trial was conducted at a UK 'centre of excellence'. It is unclear whether these findings are applicable to 'ordinary' clinical settings.
- **Availability of treatment:** CBT is a specialist treatment, and there is a dearth of qualified therapists. However, CBT for bulimia nervosa has been successfully delivered as a book and incorporated into stepped care guidelines (CBT self-help > group CBT > individual CBT).
- **Acceptability of treatment:** All psychotherapies, including CBT and BT, rely upon patient motivation, in order to be effective. Therefore, engagement by the patient is crucial.
- **Duration of effect:** Participants were assessed only at the end of treatment, rather than at intervals (e.g. 1 or 2y). It is not clear whether the beneficial effects of CBT endure and whether intermittent 'booster' CBT sessions help.

Eating disorders (anorexia and bulimia nervosa): family therapy

An evaluation of family therapy in anorexia nervosa and bulimia nervosa.

AUTHORS: Russell G, Szmukler G, Dare C *et al.*

REFERENCE: *Arch Gen Psychiatry* (1987) **44**, 1047–56.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Family therapy (FT) has a role in the treatment of younger patients with severe eating disorders.

Impact

There is a paucity of randomized evidence to inform the management of anorexia nervosa. However, FT focused on the eating disorder remains a firm treatment option for younger patients with anorexia nervosa.

Aims

At the time of this trial, FT was frequently advocated for the treatment of anorexia nervosa, despite a lack of good evidence. This trial aimed to compare the effectiveness of two therapies (family-oriented and non-family-oriented), which were matched for form, duration, and intensity in the treatment of severe (hospitalized) eating disorders.

Methods

Patients: 80 patients at one centre in the UK (57 had anorexia nervosa, and 23 bulimia nervosa).

Inclusion criteria:

- Meet DSM criteria for anorexia nervosa and bulimia nervosa;
- Admitted to a specialist eating disorder treatment unit;
- Either gender.

Groups: All participants received inpatient care, focused on restoring weight, of an average 10wk. Patients were then randomized to the following treatments, and treatment continued as an outpatient for 1y from discharge. Treatments were matched for therapist input:

- FT: involving all immediate family members; three defined tasks and three defined phases of treatment ($n = 41$);
- Individual therapy (IT): with supportive, educational, cognitive, and problem-oriented elements ($n = 39$).

Endpoints:

- General outcome, based on weight and menstrual status (good/intermediate/poor);
- Morgan and Russell scales for anorexia nervosa;
- Need for readmission.

Follow-up: At discharge, 3, 6, and 9mo and (primary endpoint) at 1y.

Results

Table 15.6 Summary of results

| Good vs intermediate/poor outcomes (at 1y) | FT | IT | p |
|--|------|------|-------|
| In AN onset <19, duration <3y | 6/10 | 1/11 | <0.02 |
| In AN onset <19, duration >3y | 2/10 | 2/9 | ns |
| In AN onset >18 | 0/7 | 2/7 | ns |
| In BN | 0/9 | 1/10 | ns |

AN, anorexia nervosa; BN, bulimia nervosa.

Discussion

The study provided some evidence for the effectiveness of FT in young (age ≤ 18 y) patients with anorexia nervosa of recent onset (<3y). However, there was no evidence for its effectiveness, compared to IT in young and more chronic patients, in older patients, or in bulimia nervosa. (See Table 15.6.)

Problems

- **Study complexity:** The manuscript is complex, as is typical of RCTs from the 1980s. Additionally, the presentation of findings for each of the four subgroups complicates interpretation.
- **Applicability:** This trial was conducted in a ‘centre of excellence’; it is unclear whether the findings can be generalized to other settings.
- **Acceptability:** There were dropouts from treatment in both groups, and dropouts had a worse outcome. This emphasizes the crucial role of patient engagement in the management of eating disorders.
- **Sample size:** The study was small. However, there is a lack of randomized evidence on which to base treatment for this common disorder, which has a high rate of suicide and medical complications.

Attention-deficit/hyperactivity disorder: medication

MTA (Multimodal Treatment study of children with ADHD) study: A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder.

AUTHORS: The MTA Cooperative Group.

REFERENCE: *Arch Gen Psychiatry* (1999) 56, 1073–86.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Stimulant medications are superior to behavioural treatment in the management of attention-deficit/hyperactivity disorder (ADHD).

Impact

Stimulant medications (e.g. methylphenidate, atomoxetine, dexamfetamine) are now a mainstay of ADHD management. UK prescribing of stimulants for ADHD doubled between 1998 and 2004.

Aims

ADHD affects about 5% of children and adolescents, some of whom require treatment. At the time of this trial, there was poor evidence for the use of stimulants, especially regarding the duration and context of treatment, and the co-prescription of behavioural therapy. Therefore, this study aimed to compare the long-term efficacy of pharmacotherapy, behaviour therapy, and the combination, compared to usual care in ADHD.

Methods

Patients: 579 children recruited through six teams at multiple centres in the USA (4,541 potential participants screened for inclusion).

Inclusion criteria:

- Age 7–9.9y (school grades 1–4);
- Resident with same 1° carer(s) for ≥ past 6mo;
- DSM-IV combined-type ADHD.

Exclusion criteria:

- Situations preventing family's full participation in assessment or treatment;
- Might require additional treatments incompatible with study regime.

Groups:

- Medication management (methylphenidate or alternatives) ($n = 144$);
- Behavioural treatment (parent training, therapeutic summer camp, school-based interventions) ($n = 144$);
- Combined treatment ($n = 145$);
- Community care (treatment as usual) ($n = 146$).

Outcome domains assessed: Teacher and parent assessments:

- ADHD symptoms, including inattention and hyperactivity–impulsivity;
- Other symptoms, including oppositional/aggressive and internalizing;
- Social skills, parent–child relations.

Follow-up: At 14mo.

Results

- Medical management was superior to behavioural intervention/usual care for core ADHD symptoms of inattention, hyperactivity, and impulsivity ($p = 0.001$);
- Combination treatment was superior to behavioural treatment alone (but not better than medical management alone) for ADHD symptoms, oppositional/aggressive behaviours, internalizing, and academic achievement;
- Combination treatment was better than usual care in all domains assessed.

Discussion

This landmark study convincingly demonstrated the key role of medication in the management of ADHD. The adequate sample size, duration, and broad range of outcomes assessed avoided some of the common pitfalls of such studies. The lack of substantial benefit from supplementing medical management with specific and intensive behavioural treatments was surprising at the time. However, it should be noted that medical management received by participants was not simply adjustment of prescriptions; it involved monthly half-hour reviews, including practical advice and support.

Problems

- Efficacy of specific medicines: The medication protocol involved several different agents, so any differences between them may have been obscured.
- Applicability: The time and resources to emulate this study may not be widely available.
- Use and abuse of stimulants: The increasing use of stimulants among children is controversial.

Chronic fatigue syndrome: non-pharmacological treatments

The PACE Study: Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE).

AUTHORS: White P, Goldsmith K, Johnson A et al.

REFERENCE: *Lancet* (2011) 377, 823–36.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

CBT and graded exercise therapy (GET), but not adaptive pacing therapy (APT), lead to moderate improvement in outcomes, when used alongside specialist medical care, for the treatment of people with chronic fatigue syndrome (CFS).

Impact

CFS was, for years, an illness without an effective treatment. CBT and GET are now core options for treatment. This trial demonstrates the role of structured psychological interventions, targeting cognitions (thoughts and beliefs about symptoms, health, and illness) and behaviours (including activity levels and patterns) in the management of many medically unexplained symptoms and syndromes.

Aims

CFS is a common and disabling disorder. Yet, until recently, there have been few RCTs of possible treatments. In part, this was due to continuing uncertainty and controversy regarding the aetiology, reflected in the number of active treatments in this trial. The authors aimed to determine the comparative effectiveness and safety of four commonly used treatments.

Methods

Patients: 641 new patients at six specialist CFS outpatient clinics in the UK.

Inclusion criteria:

- Age >17y;
- With CFS (diagnosed by Oxford criteria; main complaint of fatigue, with bimodal Chalder score >5; significant disability, defined as Short Form-36 Physical Function (SF-36 PF) score of <61; no explanatory medical or psychiatric diagnosis, following medical assessment by a specialist);
- Without significant risk of self-harm.

Groups: Up to 15 sessions of manualized treatment:

- Specialist medical care (SMC) only: Explanation, generic advice, specific advice on self-help, symptomatic pharmacotherapy ($n = 160$);
- SMC + APT: Views CFS as an organic disease process, in which there is a finite amount of energy available, and trains the patient to function optimally within those limits ($n = 160$);

- SMC + GET: Regards CFS as being reversible and arising from activity avoidance and resulting physical deconditioning ($n = 160$);
- SMC + CBT: Regards CFS as being reversible and focuses on 'unhelpful' cognitions (e.g. activity will make me worse) and behaviours (activity avoidance) ($n = 161$).

Primary endpoint: 'Clinically useful difference' between means of the primary outcomes (2-point change in Chalder fatigue score/8-point change in SF-36 PF score).

Secondary endpoints:

- CGI scale; distance achieved in 6min walking test; disturbed sleep scale; HAD scale—anxiety and depression; work and social adjustment scale.

Follow-up: At randomization, 12wk, 24wk, and 52wk.

Results

Table 15.7 Summary of results

| Primary endpoint (at 52wk) | SMC only | SMC + APT | SMC + GET | SMC + CBT |
|----------------------------|--------------|---------------|--------------|--------------|
| Improved | 68/152 (45%) | 64/153 (42%) | 94/154 (61%) | 87/148 (59%) |
| ARR, vs SMC only | | −0.03 | 0.16 | 0.14 |
| 95% CIs | | −0.14 to 0.08 | 0.05–0.27 | 0.03–0.25 |
| NNT, vs SMC only | | −34 | 6 | 7 |
| 95% CIs | | −7 to 12 | 3–19 | 4–35 |

Discussion

There is now convincing trial evidence for moderate benefits of CBT/GET in 'typical' patients presenting to 2° care with chronic unexplained fatigue. However, the use of 'psychological' treatments for a 'physical' disorder is controversial, and not universally accepted by patients and patient groups. Persuading patients of the wisdom of this course takes time and skill. Criticism of this study has been vigorous and well organized (e.g. see *BMJ* (2013) 347, f5731 and f5963). (See Table 15.7.)

Problems

- Availability: CBT/GET need to be delivered by trained therapists (but not necessarily clinical psychologists/physiotherapists). However, there is a lack of appropriate expertise, resulting in long waits for treatment in the UK and elsewhere. There is a need for evidence on the effectiveness of scalable interventions, e.g. groups.
- Possibility of differential response of subgroups: It is possible that CFS comprises different subgroups, some of which will respond well to CBT/GET and others which may not. Indeed, some argue that CBT/GET can be actively detrimental to well-being, although there is no good evidence to support this.

Renal medicine

Introduction 420

Acute renal failure: renal replacement therapy 422

Chronic kidney disease: protein restriction and blood pressure control 424

Chronic kidney disease: erythropoietin-stimulating agents and cardiovascular risk 426

Chronic kidney disease: statins, ezetimibe, and cardiovascular risk 428

Dialysis: timing of initiation 430

Dialysis: cardiovascular effects of cinacalcet 432

Non-diabetic nephropathy: ACE inhibitors 434

Glomerulonephritis: membranous nephropathy and immunosuppression 436

Lupus nephritis: induction with mycophenolate mofetil vs cyclophosphamide 438

Lupus nephritis: maintenance with mycophenolate mofetil vs azathioprine 440

Polycystic kidney disease: drug interventions 442

Severe renal vasculitis: plasma exchange vs methylprednisolone 444

Introduction

Nephrology was a mid-twentieth century invention. Indeed, it is about as old or young as the present leaders in the field. There had long been an interest in renal physiology and post-mortem pathology, but they were not much use in isolation. A specialty needs a clientele, a useful product, a technique, and entrepreneurial doctors. For nephrology, these were: patients with renal failure, dialysis, renal biopsy, and a remarkable cadre of determined, obsessional, and obstinately optimistic physicians and surgeons. They inhabited the worlds of general medicine, hypertension, and urology, before creating niches for themselves as kidney failure doctors.

Although the Renal Association started in 1950, the International Society of Nephrology was only created in 1960. The success of dialysis and transplantation as treatments for 'terminal renal failure' (as it was once called) are among the outstanding achievements in medicine in the last 50y. Their development bypassed business plans, risk assessments, protocols, and SWOT (Strengths, Weaknesses, Opportunities, and Threats) analyses that paralyse attempts at innovation today.

Treatment of renal disease with drugs, such as corticosteroids and anti-metabolites, was empirical. Successful though these treatments may be, we do not really know whether we are applying them in the best way. Doing randomized trials of effective treatments is tricky, especially as many nephrologists are supremely confident they have identified the right way to do things. Slowly this mindset is being changed, prejudices are being challenged, and old, as well as new, treatments properly tested. The renal pharmacopoeia has been, and is being, added to regularly with biologics such as the erythropoiesis-stimulating agents (ESAs), immunosuppressant monoclonals, and designer agonists such as calcimimetics. These are exciting times for clinical research, and depressing ones for health economists.

This section describes some of the investigations that have persuaded some clinicians to change some of what they do some of the time.

Acute renal failure: renal replacement therapy

Intensity of renal support in critically ill patients with acute kidney injury.

AUTHORS: The VA/NIH Acute Renal Failure Trial Network.

REFERENCE: *N Engl J Med* (2008) **359**, 7–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Outcome of acute kidney injury in the ICU setting is not improved by increasing the dose of renal replacement therapy (RRT).

Impact

The dose of RRT does not appear to be a limiting factor in the survival of patients on ICU with acute kidney injury.

Aims

Acute renal failure (ARF), commonly part of multiorgan failure, occurs frequently in critically ill patients. It is characterized by a sustained decline in the glomerular filtration rate (GFR). RRT is the mainstay of treatment; however, the method and dosing of RRT still remain a subject of debate, results of previous studies having been inconsistent. This study aimed to investigate whether an increased dose of RRT in the setting of acute kidney injury on the ICU could improve patient survival.

Methods

Patients: 1,124 adult patients from 27 ICUs in the USA.

Inclusion criteria:

- Admission to ICU;
- Acute kidney injury requiring RRT;
- Failure of at least one other non-renal organ.

Groups:

- Group 1: Assigned intensive RRT (6× per wk haemodialysis or 35mL/h/kg haemofiltration) (*n* = 563);
- Group 2: Assigned standard RRT (3× per week haemodialysis or 20mL/h/kg haemofiltration) (*n* = 561).

Primary endpoint: Death from any cause by 60d after randomization.

Secondary endpoints:

- Recovery of renal function by d 28;
- Duration of RRT;
- Length of stay in ICU.

Follow-up: At 60d from randomization.

Results

Table 16.1 Summary of results

| Primary endpoint | Group | | p |
|--|-----------------|-----------------|--------------|
| | 1 | 2 | |
| Death from any cause by 60d | 302/563 (53.6%) | 289/561 (51.5%) | 0.5 |
| Secondary endpoints | | | |
| Complete recovery of renal function by 28d | 85/553 (15.4%) | 102/555 (18.4%) | Not reported |
| ICU-free days by 60d | 18.7±0.9 | 20.190.9 | 0.3 |
| Hospital-free days by 60d | 11.0±0.7 | 13.090.7 | 0.005 |

Discussion

Previous studies had reported conflicting results on the benefits of higher doses of RRT on the ICU. This study, the largest to date, used a modern optimum standard, as the control arm did not show any benefit of increasing the dose. However, the control arm therapy is often not achieved on many ICUs, so this trial should not deter such units from attempting to increase the dose of RRT to this level. (See Table 16.1.)

Problems

- Patients with pre-existing chronic kidney disease (CKD) were excluded from this study, and there is some epidemiological evidence to suggest that acute kidney injury has a distinct natural history in this group.
- The timing of initiation of RRT was not standardized, although this reflects current practice.
- The majority of patients were ♂, although no heterogeneity was apparent on the basis of gender.

Chronic kidney disease: protein restriction and blood pressure control

MDRD (Modification of Diet in Renal Disease) Study: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease.

AUTHORS: Klahr S, Levey A, Beck G *et al.*

REFERENCE: *N Engl J Med* (1994) 330, 877–84.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Protein restriction has no impact on the progression of chronic renal disease, but clear benefits are seen from strict BP control in patients with significant proteinuria.

Impact

Protein restriction is no longer recommended in the UK. This trial led the way in recommending aggressive BP control as a method of slowing the progression of CKD.

Aims

Animal models demonstrate a beneficial effect of dietary protein restriction and BP control on the progression of CKD. However, this had not been reliably demonstrated in humans. Similarly, very few trials prior to this study had investigated the effect of 'lower than usual' BP on the progression of CKD. This study included the results of RCTs, in order to test the effects of dietary protein, phosphorus intake restriction, and tight BP control on the progression of CKD.

Methods

Patients: From multiple centres in the USA—585 patients in study 1 (GFR 25–55mL/min), 255 patients in study 2 (GFR 13–24mL/min).

Inclusion criteria: CKD:

- Age 18–70y;
- Creatinine 106–619micromol/L (women), 124–619micromol/L (men);
- MAP \leq 125mmHg.

Groups:

- Study 1: Low-protein ($n = 291$) vs usual-protein diet ($n = 294$), low BP ($n = 300$) vs usual BP ($n = 285$);
- Study 2: Very low-protein ($n = 126$) vs low-protein diet ($n = 129$), low BP ($n = 132$) vs usual BP ($n = 123$);
- Usual-protein diet = 1.3g/kg/d protein; low-protein diet = 0.58g/kg/d; very low-protein diet = 0.28g/kg/d.
- Usual MAP \leq 107mmHg (age 18–60) and \leq 113mmHg (age \geq 61); low MAP \leq 92mmHg (age 18–60) and \leq 98mmHg (age \geq 61).

Primary endpoint: Rate of change of GFR.

Secondary endpoints: Rate of change of GFR in various prespecified subgroups (e.g. proteinuria <1g/d, 1–3g/d, >3g/d).

Follow-up: GFR measured (isotope method) at 2 and 4mo, and then every 4mo for a mean of 2.2y.

Results

Table 16.2 Summary of results

| Primary endpoint | | Very low protein | Low protein | Usual protein | p |
|-----------------------------------|---------|------------------|---------------|---------------|----|
| Rate of decline of GFR (mL/min/y) | Study 1 | – | 3.6 (3.1–4.2) | 4.0 (3.5–4.6) | ns |
| | Study 2 | 3.6 (2.9–4.2) | 4.4 (3.7–5.1) | – | ns |
| | | Low BP | Usual BP | | |
| | Study 1 | 3.6 (3.0–4.1) | 4.1 (3.5–4.7) | – | ns |
| | Study 2 | 3.7 (3.1–4.3) | 4.2 (3.6–4.9) | – | ns |

Discussion

This trial, the largest study of protein restriction, failed to demonstrate a durable benefit of dietary protein restriction. There was no benefit of strict BP control overall, but there was when the patients were stratified according to urinary protein excretion (strict BP control slowed progression in patients with >3g/d proteinuria in study 1 and 2). The data from this study demonstrate a strong relationship between proteinuria and the rate of progression, and contributed towards the development of strategies to reduce proteinuria as a method to slow the progression of CKD. Furthermore, the MDRD formula for estimating GFR (now used throughout the UK) was developed from the results of this study. (See Table 16.2.)

Problems

- The significant results only came from (prespecified) subgroup analysis. However, they have since been corroborated by other studies.
- The 'usual' BP target (equivalent to 140/90 and 160/90mmHg in patients under and over 60, respectively) is high by modern standards and is no longer a valid comparator for patients with CKD.
- The rate of progression in this study was slower than expected and resulted in the study being underpowered to detect the expected difference between the groups.

Chronic kidney disease: erythropoietin-stimulating agents and cardiovascular risk

TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy):

A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease

AUTHORS: The TREAT trial investigators.

REFERENCE: *N Engl J Med* (2009) **362**, 2019–32.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Darbepoetin alfa does not reduce the risk of death or CV events in pre-dialysis individuals with T2DM, CKD, and moderate anaemia.

Impact

Darbepoetin alfa has no impact upon CV risk in patients with T2DM and CKD.

Aims

T2DM and CKD are each associated with an increased risk of CV morbidity and mortality, as well as risk of progression to end-stage renal disease (ESRD). Advancing CKD is associated with the development of anaemia, due to decreased production of erythropoietin, and anaemia itself is an independent risk factor for developing CV events, especially in patients with diabetes. This double-blind, placebo-controlled RCT aimed to investigate whether increasing Hb levels with ESAs in patients with T2DM, CKD, and a moderate degree of anaemia would improve patient survival and reduce CV events and the rate of progression to ESRD.

Methods

Patients: 4,038 adult patients from 623 sites in 24 countries.

Inclusion criteria:

- T2DM and CKD (MDRD GFR 20–60 mL/min/1.73 m²);
- Anaemia (Hb <11 g/dL, transferrin saturation ≥15%).

Groups:

- Darbepoetin alfa (*n* = 2,012): dose adjusted according to the Hb level, aiming for 13 g/dL;
- Placebo (*n* = 2,026): delivered in a matching prefilled syringe. However, if Hb fell <9.0 g/dL, darbepoetin alfa was administered, and placebo resumed once Hb was ≥9.0 g/dL.

Primary endpoint:

- Time to composite outcome of death from any cause;
- Development of a CV event (non-fatal MI, CCF, stroke, or hospitalization for myocardial ischaemia);
- Time to death or ESRD.

Secondary endpoints:

- Rate of decline of renal function;
- Changes in fatigue and QoL by 25wk;

Follow-up: Hb levels checked fortnightly during ESA dose titration period and monthly thereafter. Transferrin saturation and ferritin levels checked 4-monthly. Other laboratory measurements and urine collections undertaken every 24wk. Patient-reported outcomes evaluated at wk 1, 13, and 25, and every 24wk thereafter.

Results**Table 16.3** Summary of results

| Primary endpoints | Darbepoetin alfa | Placebo | HR | p |
|---|-------------------|-------------------|-------------------------|-------|
| Time to death or a CV event | 632/2,012 (31.4%) | 602/2,026 (29.7%) | 1.05 (95% CI 0.94–1.17) | 0.41 |
| Time to death or ESRD | 652/2,012 (32.4%) | 618/2,026 (30.5%) | 1.06 (95% CI 0.95–1.19) | 0.29 |
| Secondary endpoints | | | | |
| Fatigue score increase of >3 points from baseline | 963/1,762 (55.2%) | 875/1,769 (49.5%) | n/a | 0.002 |
| Mean changes in scores for energy levels | 2.6 ± 9.9 points | 2.1 ± 9.7 points | n/a | 0.20 |
| Mean changes in scores for physical functioning | 1.3 ± 9.2 points | 1.1 ± 8.8 points | n/a | 0.51 |

Discussion

The results of observational studies suggesting an association between higher Hb levels and improved CV outcomes have been used to justify treating anaemia in CKD with ESAs. This study investigated whether increasing Hb levels with an ESA agent darbepoetin alfa would improve CV outcomes and mortality rates in patients with CKD and T2DM. This study did not show a decrease in the rates of CV events or the progression to ESRD with increasing Hb levels to a target of 13g/dL. Additionally, there was a significantly increased risk of both fatal and non-fatal strokes (101 with darbepoetin alfa vs 52 with placebo, $p \leq 0.001$) associated with the use of ESA. (See Table 16.3.)

Problems

- Although a well-conducted study, it has been criticized because it does not reflect current practice (e.g. Hb target of 13g/dL in the active group), but this was recommended when the trial was designed.
- It is still uncertain whether it is the Hb target or the ESA dose required to achieve that target which is harmful. However, RCTs cannot provide mechanistic information, and this trial has changed clinical practice.

Chronic kidney disease: statins, ezetimibe, and cardiovascular risk

SHARP (Study of Heart And Renal Protection) trial: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial.

AUTHORS: The SHARP trial investigators.

REFERENCE: *Lancet* (2011) 377, 2181–92.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Combination treatment with simvastatin and ezetimibe led to a significant reduction in the risk of a major vascular event occurring in patients with advanced CKD.

Impact

Patients with progressive renal failure can be treated safely with a combination of a statin and ezetimibe to significantly lower their risk of CV events and death.

Aims

The association between CKD and increased CV risk is well known. Meta-analyses looking at the beneficial effects of statin therapy in reducing CV events have found roughly 20% reduction in risk of CV events for every 1mmol/L reduction in LDL-cholesterol. However, most of the studies have excluded patients without CKD, and little is known about the effects of statins in patients with CKD. This is the largest double-blind, placebo-controlled RCT to investigate the safety and effectiveness of LDL lowering using a statin in combination with ezetimibe in patients with moderate to severe renal impairment.

Methods

Patients: 9,270 adult patients worldwide (3,023 on dialysis, 6,247 not).

Inclusion criteria:

- Age ≥ 40 y;
- Diagnosis of CKD (on the basis of >1 previous serum or plasma creatinine) ($\text{O}^\text{♂} \geq 150 \mu\text{mol/L}$, $\text{O}^\text{♀} \geq 130 \mu\text{mol/L}$);
- Dialysis patients (peritoneal dialysis and haemodialysis).

Groups: Initially randomly assigned in a 4:1:4 ratio:

- Simvastatin 20mg + ezetimibe 10mg daily ($n = 4,650$);
- Simvastatin 20mg daily (re-randomized, see below);
- Placebo ($n = 4,620$).

After 1y, those assigned to simvastatin alone were re-randomized to either simvastatin 20mg + ezetimibe 10mg or the placebo-alone group.

Primary endpoint: Development of first major atherosclerotic event (non-fatal MI, coronary death, non-haemorrhagic stroke, or requirement for any arterial revascularisation procedure not related to dialysis access).

Secondary endpoints:

- Major vascular event (non-fatal MI, cardiac death, any stroke, requirement for arterial revascularization procedure unrelated to dialysis access), major coronary event, or non-haemorrhagic stroke;
- All revascularization procedures (coronary and non-coronary);
- Time to progression to ESRD (initiation of maintenance dialysis or transplantation) among those not receiving RRT ($n = 6,247$) at time of randomization.

Follow-up: Review/blood monitoring at 2, 6, 12mo; 6-monthly thereafter for minimum of 4y. Median F/U 4.9y.

Results**Table 16.4** Summary of results

| Primary endpoint | Simvastatin + ezetimibe | Placebo | Risk ratio (RR) | <i>p</i> |
|------------------------------|-------------------------|--------------------|-------------------------|----------|
| Major atherosclerotic event | 526/4,650 (11.3%) | 619/4,620 (13.4%) | 0.83 (95%CI 0.74–0.94) | 0.0021 |
| Secondary endpoints | | | | |
| Major vascular events | 701/4,650 (15.1%) | 814/4,620 (17.6%) | 0.85 (95% CI 0.77–0.94) | 0.0012 |
| Non-haemorrhagic stroke | 131/4,650 (2.8%) | 174/4,620 (3.8%) | 0.75 (95% CI 0.60–0.94) | 0.01 |
| Major coronary event | 213/4,650 (4.6%) | 230/4,620 (5.0%) | 0.92 (95% CI 0.76–1.11) | 0.37 |
| Revascularization procedures | 284/4,650 (6.1%) | 352/4,620 (7.6%) | 0.79 (95% CI 0.68,0.93) | 0.0036 |
| Progression to ESRD | 1057/6,247 (33.9%) | 1084/6,247 (34.6%) | 0.97 (95% CI 0.89,1.05) | 0.41 |
| Vascular deaths | 361/4,650 (7.8%) | 388/4,620 (8.4%) | 0.93 (95% CI 0.80–1.07) | 0.30 |

Discussion

There was a paucity of data regarding the effectiveness of lipid lowering, in particular LDL-cholesterol lowering, in patients with progressive renal impairment, with even less data looking at the dialysis population. This was the largest study to date to investigate the beneficial effects and safety of lipid lowering with a statin in combination with ezetimibe in patients with significant renal disease. Simvastatin and ezetimibe combination resulted in a 17% risk reduction in developing a major atherosclerotic event. In addition, there was a 25% reduction in the risk of developing an ischaemic stroke, and a 21% reduction in revascularization procedures (predominantly coronary revascularization, 27% reduction, $p = 0.0027$). There was no increase in the risk of progression to ESRD. Combination treatment was well tolerated, with no significant risk of myopathy, hepatitis, gallstones, or cancer in the treatment group. (See Table 16.4.)

Problems

The effect of lowering LDL-cholesterol in pre-dialysis and dialysis patients was similar (p for heterogeneity = 0.25). However, some interpret the lack of significance within the dialysis subgroup alone (RR 0.90, 95% CI 0.75–1.08) as evidence that lowering LDL is not beneficial in dialysis patients. However, this is an inappropriate subgroup analysis, and the test for heterogeneity above shows that the overall beneficial treatment effect does not differ by baseline dialysis status. Furthermore, a substantially increased CV risk in the dialysis population means that even a small relative effect translates into a worthwhile absolute benefit.

Dialysis: timing of initiation

IDEAL (Initiating Dialysis Early And Late) study: A randomized, controlled trial of early versus late initiation of dialysis.

AUTHORS: The IDEAL Trial Investigators.

REFERENCE: *N Engl J Med* (2010) **363**, 609–19.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Starting dialysis early (i.e. at a higher level of renal function) is not associated with improved patient survival or dialysis-related co-morbidity outcomes, compared to a later start.

Impact

The decision regarding when to start dialysis should be based upon patients' symptoms, rather than a particular eGFR target.

Aims

The exact timing of initiation of dialysis remains a contentious issue. Conventionally, the decision to start dialysis has centered on a patient's signs and symptoms of uraemia, in combination with their biochemical profile. However, recent studies have ignited fresh debate as to the appropriate timing of initiating dialysis, with some observational data proposing that starting dialysis early leads to improved survival and QoL outcomes, and other data suggesting it may actually be detrimental. This study aimed to investigate in a randomized trial the morbidity and mortality outcomes of an 'early start' vs a 'late start' on dialysis.

Methods

Patients: 828 patients from 32 centres in Australia and New Zealand.

Inclusion criteria:

- Age $18 \geq y$;
- Progressive CKD or failing kidney transplant;
- eGFR calculated using the Cockcroft–Gault equation of $10.0\text{--}15.0\text{ mL/min/1.73m}^2$ of BSA.

Groups: Patients initially randomly assigned to one of two groups:

- 'Early-start' ($n = 404$): start dialysis when eGFR $10.0\text{--}14.0\text{ mL/min/1.73m}^2$;
- 'Late-start' ($n = 424$): start dialysis when eGFR $5.0\text{--}7.0\text{ mL/min/1.73m}^2$; continue routine medical care until then.

NB. Patients in the late-start category could be started at eGFR $>7.0\text{ mL/min/1.73m}^2$, if deemed necessary by the patients' usual physician.

Primary endpoint: Death from any cause.

Secondary endpoints:

- CV events (CV death, non-fatal MI and stroke, new-onset angina, TIA);
- Infection-related events;
- Death or hospitalization due to any infection-related event;
- Complications of dialysis (need for temporary dialysis catheter; revision of dialysis access, infection of the dialysis access site, or an electrolyte or fluid status disorder requiring hospital admission, additional dialysis, or both).

Follow-up: Continued until 1y after randomization (which was between July 2000 and November 2008). Median duration of F/U 3.64y in early-start group and 3.57y in late-start group.

Results

- A total of 322 (75.9%) patients in the late-start group started dialysis at an eGFR $>7.0\text{mL/min/1.73m}^2$ due to onset of symptoms (mean starting GFR 9.8mL/min , compared to 12.0mL/min in the early-start group);
- Median time from randomization to starting dialysis: early-start = 1.8mo (95% CI 1.60–2.23), late-start = 7.4mo;
- A total of 59 randomized patients had not started dialysis by trial end. (See Table 16.5.)

Table 16.5 Summary of results

| Primary endpoint | Early-start No. of events | Late-start No. of events | HR (early-start) | p |
|--|------------------------------|-----------------------------|-------------------------|------|
| Death from any cause | 152/404 (37.6%) | 155/424 (36.6%) | 1.04 (95% CI 0.83–1.30) | 0.75 |
| Secondary endpoints | | | | |
| Composite CV events | 139/404 (34.4%) | 127/424 (29.9%) | 1.23 (95% CI 0.97–1.56) | 0.09 |
| Composite infectious events | 148/404 (36.6%) | 174/424 (41.0%) | 0.87 (95% CI 0.70–1.08) | 0.20 |
| Dialysis complications | | | | |
| Insertion of a temporary dialysis catheter | 118/404 (29.2%) | 124/424 (29.2%) | 1.03 (95% CI 0.80–1.32) | 0.85 |
| Revision of dialysis access | 145/404 (35.9%) | 147/424 (34.7%) | 1.08 (95% CI 0.85–1.35) | 0.54 |
| Access-site infection | 47/404 (11.6%) | 50/424 (11.8%) | 0.99 (95% CI 0.67–1.48) | 0.97 |
| Fluid or electrolyte disorder | 146/404 (36.1%) | 175/424 (41.3%) | 0.88 (95% CI 0.71–1.10) | 0.26 |
| Death from treatment withdrawal | 24/404 (5.9%) | 22/242 (2.5%) | 1.17 (95% CI 0.66–2.08) | 0.60 |

Discussion

Many studies have tried to address the issue of appropriate timing of starting dialysis. However, with mixed results, the question of timing remains uncertain. This study did not show any significant survival benefit with starting dialysis early, rather than late, even among patients with a failing transplant. There was also no improvement in CV events, infection-related events, dialysis complications, or QoL assessments with an early start on dialysis. The decision when to initiate dialysis therapy should not be based on a particular level of GFR, but rather patient symptoms and signs of uraemia and other complications of ESRD.

Problems

- This was a relatively ‘young’ (median age 60y) and predominantly white Australasian cohort, with very few patients from ethnic minority groups. This may affect wider applicability of the results.
- Three-quarters of patients in the late-start group initiated dialysis at a higher GFR than the target of $>7.0\text{mL/min/1.73m}^2$, leaving a difference of only 2.2mL/min between the two mean start GFRs.
- Far more patients on peritoneal dialysis than haemodialysis in this study, compared with UK patterns of dialysis preferences.

Dialysis: cardiovascular effects of cinacalcet

EVOLVE (Evaluation **O**f Cinacalcet Hydrochloride Therapy to **L**ower Cardio**V**ascular **E**vents) trial: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis.

AUTHORS: The EVOLVE Trial Investigators.

REFERENCE: *N Engl J Med* (2012) **367**, 2482–94.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Cinacalcet has no benefit as an agent to reduce risk of death or CV events in 2° hyperparathyroidism, but the play of chance caused an important imbalance in the baseline age between the two randomized groups, raising doubts about this conclusion.

Impact

The benefits of intervening on bone mineral metabolism in dialysis patients remain uncertain.

Aims

Data from observational studies of patients undergoing dialysis suggest there is an association with increased risk of death and CV events in those with elevated serum levels of calcium (Ca), phosphate (P), PTH, and fibroblast growth factor 23 (FGF23). It is thought that disorders of bone and mineral metabolism result in arterial calcification and increased vascular resistance, which can lead to myocardial ischaemia, cardiac failure, and sudden cardiac death. Cinacalcet is a drug that acts on the calcium-sensing receptor of the parathyroid glands, resulting in reduced levels of PTH and calcium. Small-scale studies looking at cinacalcet have found reductions in vascular and valvular calcification. This study aimed to investigate whether treating dialysis patients with 2° hyperparathyroidism with cinacalcet would reduce their risk of death and non-fatal CV events.

Methods

Patients: 3,883 dialysis patients from multiple worldwide centres.

Inclusion criteria:

- Age ≥ 18 y;
- On 3 \times weekly maintenance haemodialysis for >3 mo prior;
- Following biochemical parameters confirmed from a central laboratory: serum calcium ≥ 2.1 mmol/L; serum PTH ≥ 31.8 pmol/L; Ca \times P ≥ 3.63 mmol²/L².

Groups:

- Cinacalcet ($n = 1,948$);
- Placebo ($n = 1,935$)

Primary endpoint: Composite endpoint of time to death or until the first non-fatal CV event (including MI or hospitalization for myocardial ischaemia, cardiac failure, or peripheral vascular disease related co-morbidity).

Secondary endpoints:

- Death related to a CV event, including stroke;
- Time to development of any one of the primary endpoints;
- Bone fractures;
- Need for parathyroidectomy.

Follow-up: Every 4wk during initial 20wk drug escalation period, then 8-weekly thereafter for 64mo (until 6mo after discontinuation of drug). Median study drug F/U 21.2mo.

Results**Table 16.6** Summary of results

| Primary endpoint | Cinacalcet | Placebo | HR | p |
|----------------------------|-------------------|-------------------|-------------------------|------|
| Primary composite endpoint | 938/1,948 (48.2%) | 952/1,935 (49.2%) | 0.93 (95% CI 0.85–1.02) | 0.11 |
| Secondary endpoints | | | | |
| Stroke | 115/1,948 (5.9%) | 102/1,935 (5.3%) | 1.07 (95% CI 0.82–1.40) | 0.61 |
| Death—CV event | 377/1,948 (19.4%) | 391/1,935 (20.2%) | 0.92 (95% CI 0.80–1.07) | 0.28 |
| Fractures | 238/1,948 (12%) | 255/1,935 (13%) | 0.89 (95% CI 0.75–1.07) | n/a |
| Parathyroidectomy | 140/1,948 (7%) | 278/1,935 (14%) | 0.44 (95% CI 0.36–0.54) | n/a |

Discussion

Several studies have suggested a possible link between disorders of bone and mineral metabolism and excess risk of death and CV events in patients with ESRD, possibly via structural changes within the vascular system. This study was the largest to date to assess whether treatment with cinacalcet, a calcimimetic agent, would be beneficial in reducing the risk of death and CV events in patients on haemodialysis with moderate to severe 2° hyperparathyroidism. The study failed to demonstrate a significant benefit of using cinacalcet in 2° hyperparathyroidism to reduce risk of death or CV events. This ITT analysis showed a non-significant 7% reduction in the primary composite endpoint. Critically, the cinacalcet population was 1y older than the placebo group, and age is a very strong risk factor for CV events and mortality. After adjustment for this, the analysis showed a significant reduction in the primary endpoint (HR 0.88, 95% CI 0.79–0.97, $p = 0.008$). This suggests cinacalcet may indeed be a beneficial drug in this population. However, the treatment was poorly tolerated, with a significant number of adverse events, predominantly related to GI symptoms (nausea, vomiting, diarrhoea) and hypocalcaemia. This study did not demonstrate a benefit of using cinacalcet in lowering the excess risk of CV events or death in patients undergoing haemodialysis. (See Table 16.6.)

Problems

- High rates of study drug discontinuation (62%, 1,207/1,948) and dropout rates related to substantial number of adverse events associated with treatment with cinacalcet (including GI symptoms and hypocalcaemia).
- 19.8% within the placebo group were also receiving commercially available cinacalcet, further reducing the statistical power of the study.
- The effect on mortality was similar across all causes—an unusual finding. Cinacalcet might be expected to reduce CV mortality, but why it should reduce the risk of dying of other diseases is unclear.

Non-diabetic nephropathy: ACE inhibitors

REIN (Ramipril Efficacy In Nephropathy) study: Randomised placebo-controlled trial of the effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy.

AUTHORS: GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia).

REFERENCE: *Lancet* (1997) **349**, 1857–63.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Ramipril slows the rate of decline of GFR in patients with non-diabetic nephropathy and proteinuria of $\geq 3\text{g/d}$.

Impact

The findings extended the indication for ACE-Is to all patients with proteinuria, not just those with diabetic nephropathy. The benefit of ACE-Is was more than expected for the degree of BP lowering.

Aims

GFR usually continues to decline, despite treatment of the original causative factor in most forms of proteinuric chronic renal disease. HTN is likely to have the largest contribution to this renal dysfunction. ACE-Is are known to reduce both urinary protein excretion and BP. However, the differential contribution of these two effects towards slowing the decline in GFR had been unclear. This study was designed to investigate this further.

Methods

Patients: 352 patients at 14 Italian centres.

Inclusion criteria: Non-diabetic proteinuric nephropathy:

- Age 18–70y;
- Measured GFR $15\text{--}70\text{mL/min/1.73m}^2$;
- Urinary protein excretion $>1\text{g/24h}$ for at least 3mo.

Groups:

- Stratum 1: proteinuria $1\text{--}2.9\text{g/24h}$ (results not published);
- Stratum 2: proteinuria $\geq 3\text{g/24h}$ —ramipril ($n = 78$), placebo ($n = 88$).

Primary endpoint: Effect of allocation to ramipril or placebo on rate of decline in GFR.

Secondary endpoints:

- Degree of proteinuria;
- Time to doubling of serum creatinine or progression to end-stage renal failure (ESRF);
- Major CV complications;
- Total and CV mortality rate.

Follow-up: GFR measured (by iohexol clearance) at 1, 3, and 6mo after randomization, and then 6-monthly. Stratum 2 was stopped early (after mean F/U of 16mo) and published in this report.

Results**Table 16.7** Summary of results

| Primary endpoint | Ramipril | Placebo | p |
|-----------------------------------|-------------------------|---------------------|------|
| GFR/mo (mL/min) | -0.53 (\pm 0.08) | -0.88 (\pm 0.13) | 0.03 |
| Secondary endpoints | | | |
| Urinary protein excretion (g/24h) | Not adequately reported | | |
| Doubling serum creatinine or ESRF | 18 | 40 | 0.02 |
| SBP (mean) (mmHg) | 144.0 (\pm 1.8) | 144.6 (\pm 1.5) | 0.9 |
| Diastolic BP (mean) (mmHg) | 88.2 (\pm 0.9) | 88.9 (\pm 0.9) | 0.6 |

Discussion

This study demonstrated a benefit of ACE-Is on proteinuric non-diabetic nephropathy, independent of their BP-lowering effect. However, this report only related to the strata of patients with more marked proteinuria ($\geq 3\text{g}/24\text{h}$), as the benefit was only apparent in the interim analysis of this population. The study also demonstrated that ACE-Is were safe in this population, with hyperkalaemia only being reported in two patients (one in the ramipril group, one in the placebo group). (See Table 16.7.)

Problems

- The study was stopped early, based on an interim analysis of only 87 patients, which increased the risk of chance affecting the results.
- Data concerning the effect of ramipril on urinary protein excretion were inadequately reported. Although the change in protein excretion in the ramipril group was significant (and was not significant in the placebo group), it is the difference in the change between the two groups that is critical. This was not reported.
- A later publication of the data from patients in stratum 1 did not demonstrate a benefit in terms of the primary outcome, but did demonstrate a benefit in terms of progression to ESRF.

Glomerulonephritis: membranous nephropathy and immunosuppression

Immunosuppression for progressive membranous nephropathy: a UK randomized controlled trial.

AUTHORS: Howman A, Chapman TL, Langdon MM *et al.*

REFERENCE: *Lancet* (2013) **381**, 744–51.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Patients with idiopathic membranous nephropathy and declining renal function should be treated for 6mo with prednisolone and chlorambucil.

Impact

Treatment with prednisolone and chlorambucil is superior to ciclosporin or supportive treatment alone in patients with idiopathic membranous nephropathy.

Aims

Membranous nephropathy frequently presents with nephrotic syndrome and is a significant cause of ESRD in about a third of affected individuals. The condition is often treated with immunosuppressive drug therapies, which have significant adverse effects. However, the ideal treatment regimen remains unclear. This study aimed to investigate whether prednisolone and chlorambucil or ciclosporin was superior to supportive therapy alone in preserving declining renal function in individuals with idiopathic membranous nephropathy.

Methods

Patients: 108 adult patients from 37 renal units within the UK.

Inclusion criteria:

- Age 18–75y;
- Biopsy-proven idiopathic membranous nephropathy;
- Serum or plasma creatinine of $<300\mu\text{mol/L}$ and a decline in renal function of $\geq 20\%$, based on ≥ 3 measurements of renal function between 3mo and 2y before entry into the study.

Groups:

- Supportive therapy (ST) with 6mo of additional treatment with prednisolone and chlorambucil ($n = 33$);
- Supportive therapy with 12mo of ciclosporin ($n = 36$);
- Supportive therapy alone (including ACE-Is, statins, and anticoagulants, if required) ($n = 37$).

Primary endpoint: A calculated decline in renal function by a further 20% from baseline renal function, using the Cockcroft–Gault formula.

Secondary endpoints:

- Occurrence of serious adverse events;
- Degree of proteinuria.

Follow-up: Minimum 3y or until primary endpoint reached. Surviving patients remain under routine nephrology clinic F/U.

Results**Table 16.8** Summary of results

| Primary endpoint | Prednisolone + chlorambucil + ST | Ciclosporin + ST | Standard therapy alone |
|---|---|---|------------------------|
| Risk of further 20% decline in renal function | 19/33 (58%) (HR 0.44, 95% CI 0.24–0.78, $p = 0.0042$) | 29/36 (81%) (HR 1.17, 95% CI 0.70–1.95, $p = 0.54$) | 31/37 (84%) |
| Secondary endpoints | | | |
| Reduction in proteinuria over time | –2.2g/24h ($p = 0.014$) | –0.7g/24h ($p = 0.46$) | |
| Number of patients suffering from a serious adverse event by 1y | 17/33 (52%) ($p = 0.048$) | 17/37 (46%) ($p = 0.20$) | 11/38 (29%) |

- Significant difference in the number of patients who reached the primary endpoint across all three groups, $p = 0.003$ (See Table 16.8.)

Discussion

The best immunosuppression strategy for the management of idiopathic membranous nephropathy remained unclear among nephrologists. This study was the first prospective RCT to review the effects of immunosuppressive therapy in patients with declining renal function. A combined treatment of supportive interventions with prednisolone and chlorambucil was better at preventing progressive decline in renal function in this specific subset of patients. However, this therapy is not without significant adverse events, particularly haematological, and thus more effective and less toxic treatments are required for this condition.

Problems

- Small-scale study with only 108 patients. There was a very long study duration, during which time additional therapies have emerged which could be potentially less toxic (cyclophosphamide, rituximab), compared with chlorambucil.
- The timing of initiation of therapy between the supportive and intervention groups was not standardized, causing a potential risk of bias.
- Furthermore, ciclosporin causes an acute reduction in GFR, which may have contributed to the excess of 1° events in the ciclosporin group. However, the timing of these events suggests that this was not a major contributor.

Lupus nephritis: induction with mycophenolate mofetil vs cyclophosphamide

ALMS (Aspreva Lupus Management Study): first phase – induction therapy: Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis.

AUTHORS: The ALMS Trial Investigators.

REFERENCE: *J Am Soc Nephrol* (2009) 20, 1103–12.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Mycophenolate mofetil (MMF) is not superior to IV cyclophosphamide (IVCP) for induction of remission in patients with active lupus nephritis (LN).

Impact

IVCP remains the first-line induction therapy for patients with active LN.

Aims

Systemic lupus erythematosus (SLE) is complicated by LN in about two-thirds of cases and is a poor prognostic marker. Monthly IVCP therapy had been the standard for remission induction in active LN since the 1970s, following the National Institute of Health (NIH) studies. However, this treatment is associated with significant adverse effects (e.g. increased risks of infection, bladder cancer, and gonadal toxicity). Furthermore, the response rates of LN are variable. Small studies had suggested MMF to be superior to IVCP for induction of remission and maintenance treatment. This aimed to be the largest prospective study to investigate whether MMF was superior to IVCP, for remission induction in patients with certain LN classes.

Methods

Patients: 370 patients from 88 centres in 20 countries worldwide.

Inclusion criteria:

- Age 12–75y;
- Diagnosis of SLE (American College of Rheumatology criteria);
- Biopsy-proven (in past 6mo) active or active + chronic LN (International Society of Nephrology (ISN)/Renal Pathology Society (RPS) 2003 criteria) classes: III (focal LN), IV-S (diffuse segmental), IV-G (global), V (membranous), III + V, IV + V. Class III or V patients also required to have $\geq 2\text{g}/24\text{h}$ of proteinuria.

NB. IV corticosteroid pulses were prohibited during the 2wk prior to study randomization and throughout the study duration.

Groups:

- Oral MMF bd ($n = 185$): target dose 1.5g bd (min. 2g/d, if not tolerated)—starting dose 500mg bd in wk 1, increased to 1g bd in wk 2, and aiming to achieve target dose in wk 3;
- Monthly IVCP pulse ($n = 185$): 0.5–1.0g/m², as per modified NIH protocol.

Treatment induction phase: 24wk. Both groups received additional tapering corticosteroids doses (max. starting dose 60mg/d).

Primary endpoint: Clinical response during induction period:

- Fall in urine protein/creatinine ratio (uPCR) to <3g/24h (patients with nephrotic-range proteinuria) or $\geq 50\%$ (patient with baseline proteinuria <3g/24h); and
- Stabilized ($\pm 25\%$) or improved serum creatinine by 24wk.

Secondary endpoints:

- Complete remission, defined as return to normal serum creatinine, uPCR $\leq 0.5\text{g}/24\text{h}$, inactive urine sediment;
- Achieved any one of the above three outcomes;
- Achieved renal and extra-renal remission, i.e. (1) absence of A and B scores on British Isles Lupus Assessment Group (BILAG) scoring system, and (2) mean change in scores from Safety of Exogenous Estrogens in Lupus Erythematosus National Assessment/SLE Disease Activity Index, SELENA-SLEDAI).

Follow-up: Reviewed at wk 2 and 4, then every 4wk thereafter.

Results

Table 16.9 Summary of results

| Primary endpoint | MMF + steroids | IVCP + steroids | OR | p |
|---|-----------------|-----------------|-------------------------------------|------|
| Clinical response rate | 104/185 (56.2%) | 98/185 (53.0%) | 1.2 (95% CI 0.8–1.8) | 0.58 |
| Secondary endpoints | | | Treatment difference (%, 95% CI) | |
| Normal serum creatinine | 130/185 (70.3%) | 125/185 (67.6%) | 2.7 (–6.7 to 12.1) | ns |
| Fall in uPCR | 44/185 (23.8%) | 50/185 (27.0%) | –3.2 (–12.1 to 5.6) | ns |
| Inactive urine sediment | 58/185 (31.4%) | 44/185 (23.8%) | 7.6 (–1.5 to 16.6) | ns |
| All three above criteria met | 16/185 (8.6%) | 15/185 (8.1%) | 0.5 (–5.1 to 6.2) | ns |
| Absence of BILAG A and B scores | 54/185 (29.7%) | 45/185 (24.9%) | 4.8 (4.3–14.0) | ns |
| Change in scores from baseline and endpoint of SELENA/SLEDAI (mean \pm SD) | –6.2 \pm 10.1 | –6.6 \pm 8.0 | 0.41 (–1.48 to 2.30) | ns |
| Median daily MMF dose = 2.6g/24h; median IVCP dose per infusion = 0.75mg/m ² ; mean number of doses = 5.6 \pm 1.1. | | | | |

Discussion

Treatment of active LN is divided into two phases: remission induction and maintenance therapy. IVCP is currently used for induction of remission, but this immunosuppressive agent is associated with a significant adverse effect profile, including increased risks of infection, malignancy, and fertility problems. Less toxic treatment strategies are therefore required. In this study, MMF did not show superiority over IVCP for induction of remission nor were there any significant outcomes in the secondary endpoints. In addition, more patients withdrew treatment prematurely, due to adverse effects in the MMF arm ($n = 24$, 13%) than the IVCP arm ($n = 2413$, 7.2%) ($p = 0.07$). (See Table 16.9.)

Problems

- Small study with only 185 patients in each group.
- More people in the cohort treated with IVCP had high antibody titres and lower complement levels (reflection of disease activity) and slightly lower age at presentation and enrolment.
- A 24wk induction period may be too short for observing response to therapy and all adverse events.

Lupus nephritis: maintenance with mycophenolate mofetil vs azathioprine

ALMS (Aspreva Lupus Management Study): second phase—maintenance therapy: Mycophenolate mofetil versus azathioprine as maintenance therapy for lupus nephritis.

AUTHORS: The ALMS Trial Investigators.

REFERENCE: *N Engl J Med* (2011) 365, 1886–95.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Mycophenolate mofetil (MMF) is superior to azathioprine (AZA) for the maintenance of remission in patients with active lupus nephritis (LN).

Impact

MMF should be used first-line as a maintenance therapy in active LN.

Aims

Development of LN in SLE is a significant predictor of morbidity and mortality. Treatment of active LN occurs in two stages: firstly induction therapy to induce remission of disease, and secondly therapy to maintain remission and prevent further relapses and progression of disease. Maintenance therapy usually consists of corticosteroids with immunosuppressive agents such as MMF and AZA. This study aimed to ascertain whether there was any difference in outcomes between MMF and AZA as maintenance therapy in LN patients from the ALMS induction study.

Methods

Patients: 227 patients from 88 centres in 20 countries worldwide.

Inclusion criteria:

- Age 12–75y;
- Active LN classes III, IV (S & G), V;
- Deemed to have had a clinical response to either MMF or IVCP during the induction study.

Groups:

- Oral MMF 1g bd ($n = 116$);
- Oral AZA 2mg/kg body weight od ($n = 110$).

NB. Patients with body weight <50kg or unable to tolerate the target dose were allowed to reduce doses to a minimum of MMF 1g bd or AZA 50mg od. Both groups were allowed to receive additional corticosteroids, as required, to a maximum dose equivalent to prednisolone 10mg od.

Primary endpoint: Time to treatment failure.

Secondary endpoints:

- Time to reaching ESRD;
- Time to sustained doubling of serum creatinine;
- Time to renal flare: nephritic ($\geq 25\%$ rise in serum creatinine + doubling of urine protein clearance to minimum of 2g/24h; new/worse

microscopic haematuria; or development of cellular casts) or proteinuric (doubling of uPCR);

- Time to requiring 'rescue therapy' (further immunosuppressive agents, including glucocorticoids, IV Ig, plasma exchange).

Follow-up: Reviewed at mo 0, 1, and 2, then 3-monthly thereafter until 36mo, early withdrawal from the trial, or treatment failure.

Results

Table 16.10 Summary of results

| Primary endpoint | MMF | AZA | HR | <i>p</i> |
|--------------------------------|----------------|----------------|-------------------------|----------|
| Time to treatment failure | 19/116 (16.4%) | 36/111 (32.4%) | 0.44 (95% CI 0.25–0.77) | 0.003 |
| Secondary endpoints | | | | |
| Time to renal flare | 15/116 (12.9%) | 26/111 (23.4%) | 0.50 (95% CI 0.26–0.93) | 0.03 |
| Major extra-renal flare | 8/116 (6.9%) | 7/111 (6.3%) | –3.2 (–12.1 to 5.6) | 0.94 |
| Time to 'rescue therapy' | 9/116 (7.8%) | 19/111 (17.1%) | 0.39 (95% CI 0.18–0.87) | 0.02 |
| Time to doubling of creatinine | 1/116 (0.9%) | 5/111 (4.5%) | Not recorded | 0.07 |
| Time to ESRD | 0/116 (0%) | 3/111 (2.7%) | Not recorded | 0.07 |

Mean dose (SD): MMF = 1.87g (\pm 0.43); AZA = 119.7mg (\pm 47.91).

Discussion

In the first part of the ALMS study, MMF was not superior to IVCP in induction of remission (over 24wk) in patients with active LN, and IVCP remains the standard treatment. However, much uncertainty remains over the agent of choice to maintain remission and prevent further renal and extra-renal flares or disease progression. In this study, MMF was significantly superior to AZA in reducing the time to treatment failure, independent of the induction agent received. There were significant reductions in the rates of renal flares and requirement for additional 'rescue therapy', but there was no significant improvement in the rate of progression to ESRD. There was a much higher rate of treatment withdrawal in the AZA group than the MMF group, due to adverse events (39.6% vs 25.2%, $p = 0.02$), but, despite this, the overall incidence of adverse events was similar in both groups. (See Table 16.10.)

Problems

- Small number of patients, with even fewer completing the study (111 in MMF, only 73 completed; 116 in AZA, only 54 completed).
- Only those showing response to induction therapy were randomized, so there were far fewer black/Hispanic patients—excluding those with the highest risk of disease progression and the most difficult-to-treat disease.
- Very few with significant renal involvement (i.e. heavy proteinuria and $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), making it difficult to assess the effect of MMF or AZA in individuals with moderate to severe renal impairment.
- F/U time only 36mo, so no assumptions can be drawn on long-term benefits (e.g. CV or malignancy risk, or progression to ESRD).

Polycystic kidney disease: drug interventions

TEMPO (The Tolvaptan Efficacy and Safety in the Management of Autosomal Dominant Polycystic Kidney Disease and its Outcomes) trial: Tolvaptan in patients with autosomal dominant polycystic kidney disease.

AUTHORS: The TEMPO Trial Investigators.

REFERENCE: *N Engl J Med* (2012) 367, 2407–18.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients with autosomal dominant polycystic kidney disease (ADPKD), the use of tolvaptan, if tolerated, can slow the increase in kidney size and the decline in renal function.

Impact

Treatment with drugs, such as vasopressin V2-receptor antagonists, may offer hope to patients with ADPKD in slowing the rate of increase in renal size and decline in renal function. However, at present, the significant SE burden would be unacceptable for routine practice in the management of these patients.

Aims

ADPKD is one the leading causes of progressive decline in renal function, resulting in ESRD. The development of numerous, and often large, renal cysts can give rise to pain, infections, haematuria, HTN, and ultimately renal failure requiring RRT. Animal studies had suggested that the antidiuretic hormone arginine vasopressin and its second messenger cyclic AMP act as a promoter of renal cyst proliferation. Small non-randomized studies had suggested vasopressin V2-receptor antagonists may reduce cyst formation and the subsequent decline in eGFR. This study aimed to investigate whether tolvaptan, a vasopressin V2-receptor antagonist, would preserve renal function and reduce renal volume.

Methods

Patients: 1,445 patients from 129 centres worldwide.

Inclusion criteria:

- Age 18–50y with a diagnosis of ADPKD;
- Estimated creatinine clearance ≥ 60 mL/min (Cockcroft–Gault);
- Total kidney volume ≥ 750 mL, measured using MRI.

Groups: Randomly assigned in a 2:1 ratio:

- Tolvaptan ($n = 961$);
- Placebo ($n = 484$).

Primary endpoint: Degree of change in kidney volume.

Secondary endpoints:

- Composite markers of clinical progression (declining renal function, significant renal pain, worsening HTN, worsening albuminuria);
- Changes in the slope of renal function.

Follow-up: Weekly during dose escalation, 4-monthly during treatment, then twice (>1wk apart) after completion of treatment, for 36mo or until patients withdrew from study. Kidney MRI scans performed at baseline, at 12, 24, 36mo, or within 2wk of withdrawal (if not performed in the preceding 6mo).

Results

Table 16.11 Summary of results

| Primary endpoint | Tolvaptan | Placebo | <i>p</i> |
|---|----------------|----------------|----------|
| Increase in total renal volume/y (%) | 2.80 | 5.51 | |
| 95% CI | 95% CI 2.5–3.1 | 95% CI 5.1–6.0 | <0.001 |
| Secondary endpoints | | | |
| Slope of decline in renal function (per year mg/mL) | −2.61 | −3.81 | <0.001 |
| Composite endpoint (events/100 person-year) | 44 | 50 | 0.01 |
| Worsening renal function (events/100 person-year) | 2 | 5 | <0.001 |
| Worsening Hypertension (events/100 person-year) | 31 | 32 | 0.42 |
| Worsening albuminuria (events/100 person-year) | 8 | 8 | 0.74 |
| Significant renal pain (events/100 person-year) | 5 | 7 | 0.007 |

Discussion

ADPKD is a condition causing progressive decline in excretory renal function and eventual ESRD requiring RRT. As yet, there is no specific treatment able to slow this rate of decline. ADPKD is associated with significant co-morbidity with HTN (often requiring multiple agents) and episodes of severe pain and haematuria. This study was the largest RCT trial to date to review whether outcomes from animal studies illustrating a potential benefit of vasopressin V2-receptor antagonists, such as tolvaptan, could slow the decline of renal function by inhibiting cyst formation. Compared with placebo, tolvaptan significantly reduced the rate of increase of renal size and the decline in renal function. However, the drug was poorly tolerated, with a high discontinuation rate (23% vs 14% in the placebo group), due to problems with deranged liver function tests (which has led the US Food and Drug Administration (FDA) to restrict the licence to short-term treatment) and symptoms related to excretion of large volumes of electrolyte-free water. A new agent with a lower adverse effect profile could show promise to patients with ADPKD in slowing the rate of progression to ESRD. (See Table 16.11.)

Problems

- Study used quite a young cohort of patients, so the potential effects in the elderly, who may be at more risk of SEs, are uncertain.
- Difficult to be certain of the beneficial effects of the drug by CKD stage, what the best time to initiate treatment is, and at what point the drug is no longer beneficial, as only 25% of patients had eGFR <80mL/min.

Severe renal vasculitis: plasma exchange vs methylprednisolone

MEPEX (MEthyl Prednisolone or plasma EXchange) study: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis.

AUTHORS: Jayne D, Gaskin G, Rasmussen N et al.

REFERENCE: *J Am Soc Nephrol* (2007) **18**, 2180–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Plasma exchange is more effective than high-dose methylprednisolone in achieving renal recovery in patients with severe ARF due to anti-neutrophil cytoplasmic antigen (ANCA)-associated vasculitis.

Impact

Plasma exchange is now the standard of care for patients with severe ARF due to ANCA-positive vasculitis, in addition to standard chemotherapy with cyclophosphamide and oral steroids.

Aims

ANCA-positive systemic vasculitis (Wegener's granulomatosis or microscopic polyangiitis) is the commonest cause of rapidly progressive glomerulonephritis. Although combination therapy with cyclophosphamide and prednisolone can achieve remission in 80–90% of cases, those presenting with severe renal failure (creatinine >500 micromol/L) have poorer outcomes, only 50% having independent renal function at 1y. Therefore, this study assessed additional therapies to see if they could improve the prognosis in this group of patients.

Methods

Patients: 137 patients at 28 centres in nine European countries.

Inclusion criteria:

- Diagnosis of Wegener's granulomatosis or microscopic polyangiitis (based on standard diagnostic criteria);
- Biopsy-proven pauci-immune necrotizing glomerulonephritis;
- Serum creatinine >500 micromol/L.

Groups:

- IV methylprednisolone (1g/d, for 3 consecutive days) ($n = 67$);
- Plasma exchange (seven exchanges of 60mL/kg within 14d of study entry) ($n = 70$);
- All patients also received oral cyclophosphamide (2.5mg/kg/d, reduced to 1.5mg/kg/d at 3mo) and converted to AZA (2mg/kg) at 6mo, and oral prednisolone (starting 1mg/kg/d and tapered to 5–10mg/d) from 5 to 12mo.

Primary endpoint: Renal recovery at 3mo (defined by patient survival, dialysis independence, and serum creatinine <500micromol/L).

Secondary endpoints:

- Patient survival at 1y;
- ESRD (defined as ≥ 6 wk dialysis without subsequent recovery);
- Serum creatinine in recovering patients at 1y.

Follow-up: At 6wk, then 3, 6, and 9mo, and 1y. All patients had F/U for at least 1y.

Results

Table 16.12 Summary of results

| Primary endpoint | Methylprednisolone | Plasma exchange | <i>p</i> |
|------------------------|--------------------|-----------------|----------|
| Renal recovery at 3mo | 33/67 (49%) | 48/70 (69%) | 0.02 |
| Secondary endpoints | | | |
| Patient survival at 1y | 51/67 (76%) | 51/70 (73%) | 0.7 |
| ESRD at 1y | 22/51 (43%) | 10/51 (19%) | 0.03 |
| Serum creatinine at 1y | 198micromol/L | 199micromol/L | 0.9 |

Discussion

The benefits of plasma exchange had only previously been demonstrated by subgroup analysis of trials in patients with rapidly progressive glomerulonephritis and advanced renal failure. This trial demonstrated both a statistically significant and clinical reduction in dialysis dependence. Although plasma exchange is not inexpensive, it was certainly cost-effective, given that it halved the risk of ESRD at 12mo. (See Table 16.12.)

Problems

- Although this trial demonstrated the superiority of plasma exchange over IV methylprednisolone, it is possible that the combination would be even more efficacious.

Respiratory medicine

- Introduction 448
- Asthma: self-management 450
- Asthma: early inhaled steroid 452
- Asthma: long-acting β_2 agonist and inhaled steroid 454
- Asthma: leukotriene receptor antagonists 456
- Chronic obstructive pulmonary disease: pulmonary rehabilitation 458
- Chronic obstructive pulmonary disease: long-acting anticholinergic 460
- Chronic obstructive pulmonary disease: inhaled steroids and long-acting β_2 agonists 462
- Chronic obstructive pulmonary disease: long-term oxygen therapy 464
- Chronic obstructive pulmonary disease: non-invasive ventilation 466
- Severe emphysema: lung volume reduction surgery 468
- Treatments for smoking cessation 470
- Pulmonary embolism: post-operative prophylaxis 472
- Pulmonary embolism: type of heparin 474
- Obstructive sleep apnoea: nasal continuous positive airway pressure 476
- Small cell lung cancer: radiotherapy 478
- Non-small cell lung cancer: chemotherapy 480
- Non-small cell lung cancer: epidermal growth factor receptor inhibitors 482

Introduction

Respiratory medicine traces its origins back to chest clinics and sanatoria, which were established to cope with the epidemic killer TB. This became curable in the mid-late 1950s, involving some of the very first large-scale clinical trials. The development of lung function testing followed important advances in respiratory physiology. Radiological, cross-sectional imaging, and nuclear medicine techniques have long been applied to the lungs. Immunological, pharmacological, molecular, and genetic advances have followed.

Today, respiratory medicine is a very diverse specialty, involving common chronic diseases, rarer conditions, pulmonary involvement in systemic disorders, lung infections, tumours, and adverse drug effects. It is also an important component of general internal medicine. Respiratory medicine has been prominent in producing clinical guidelines, many of which are now evidence-based, and hence a good source of information and reference.

Asthma is the commonest chronic medical condition in the Western world, affecting all ages. Unlike most others, it is increasing in prevalence. Smoking is well established as the cause of both chronic obstructive pulmonary disease (COPD) and lung cancer, the most frequent cause of cancer death (in both sexes). Although declining, lag effects mean both conditions are increasing in prevalence and will continue to be of major importance for decades to come, particularly in the emerging Third World. Sleep medicine has long been neglected but is beginning to receive attention, and respiratory infections remain regrettably common.

Respiratory research is broad-based, but the level of government and major charity funding is scandalously low. We summarize important recent clinical papers under the subheadings asthma, COPD, infection, lung cancer, and smoking, with contributions from pulmonary vascular disease and sleep.



Asthma: self-management

Randomised comparison of guided self management and traditional treatment of asthma over one year.

AUTHORS: Lahdensuo A, Haahtela T, Herrala J et al.

REFERENCE: *BMJ* (1996) 312, 748–52.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Guided self-management using peak expiratory flow (PEF) monitoring reduces asthma events and improves overall QoL.

Impact

Self-management of asthma is now considered standard and recommended by the UK's British Thoracic Society and other international asthma management guidelines.

Aims

Some studies had reported that >70% of admissions for acute attacks of asthma could be avoided by proper prior medical care. A major problem is that patients do not react appropriately to worsening symptoms, with >50% leaving these untreated for over a week prior to admission. Guidelines do recommend self-management, although consensus on the optimal approach had yet to be reached. This study aimed to compare the efficacy of guided self-management of asthma using PEF monitoring with traditional asthma treatment over 1y in a multicentre, prospective, single-blind study.

Methods

Patients: 115 patients at three centres in Finland.

Inclusion criteria: Mild to moderate asthma:

- Adults ≥ 18 y;
- Variation of morning to evening PEF $>15\%$ on 2d in 1wk in past 6mo;
- Optimal PEF ≥ 250 L/min;
- Baseline inhaled corticosteroid (ICS) treatment, beclomethasone dipropionate (BDP) 500–2,000 micrograms/d, or budesonide 400–1,600 micrograms/d over past 6mo.

Exclusion criteria: Last course of prednisolone within 4wk.

Groups:

- Self-management group (SMG): Received education about asthma, their medication, principles of self-management, and physiotherapy techniques (over 2.5h), and their ability to monitor PEF was checked over a 1mo run-in ($n = 56$);
- Traditional asthma treatment (TAT): Shown how to use inhalers and given general asthma information (over 1h) ($n = 59$).

Primary endpoints: Asthma events, including hospital admissions, unscheduled emergency visits, days off work, courses of antibiotics and prednisolone.

Secondary endpoints: QoL focusing on asthma symptoms and sickness impact using the third part of the St George's Questionnaire (25 items), assessed at the beginning of the trial and at 4-monthly visits.

Follow-up: All patients completed at least 4mo F/U. Both groups seen at 4mo intervals for 1y. SMG patients recorded daily morning PEF, symptom score (0–3), and medication use: (1) Budesonide dose was doubled if PEF fell to <85% of optimal value. (2) Prednisolone started if PEF was <70% of optimal value.

Results

Table 17.1 Summary of results

| Primary endpoints, mean (95% CI) | SMG (n = 56) | TAT (n = 59) | p |
|----------------------------------|--------------|--------------|--------|
| Unscheduled emergency visits | 0.5 (0–4) | 1.0 (0–4) | 0.04 |
| Days off work | 2.8 (0–62) | 4.8 (0–27) | 0.02 |
| Courses of prednisolone | 0.4 (0–4) | 1.0 (0–5) | 0.006 |
| Secondary endpoints | | | |
| QoL (–50 to +50) at 1y | 16.6 (15.9) | 8.4 (18.4) | 0.009* |

* ANOVA repeated measures over 12mo. Baseline: mean age = 42y; 63% = ♀; mean FEV₁ = 2.9L (82% predicted).

Discussion

Guided self-management reduced asthma events by about 50%, compared to traditional treatment. The difference became apparent early on and increased over 1y of F/U. ICS treatment dosage and spirometry did not differ in the two groups. The thresholds of reduction from optimum PEF (15% fall for doubling ICS, and 30% for 7d course of prednisolone) were lower than previously employed. Adherence to doubling ICS was 62%, while it was 77% to starting prednisolone. Although the SMG plan was based on changes in PEF, adherence was closely related to the severity of symptoms. (See Table 17.1.)

Problems

The main therapeutic intervention of doubling ICS to prevent asthma exacerbations has been shown to be ineffective in double-blind, controlled trials, yet self-management has been shown to be effective in many (but not all) studies. No objective measure of treatment adherence in either group was available, and it is possible that self-management works by increasing compliance. The respective contributions of PEF measurement and the other components and the mechanisms of benefit are unclear. Patients with severe asthma were not included.

Asthma: early inhaled steroid

START (inhaled Steroid Treatment As Regular Therapy in early asthma) study: Early intervention with budesonide in mild persistent asthma.

AUTHORS: Pauwels R, Pedersen S, Busse W et al.

REFERENCE: *Lancet* (2003) **361**, 1071–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Long-term, once-daily inhaled low-dose budesonide decreases severe exacerbations and improves symptom control in recent-onset, mild, persistent asthma.

Impact

National and international asthma guidelines recommend the use of low-dose inhaled steroids in persistent asthma, even of recent onset and in patients with mild disease.

Aims

Airway inflammation is a major determinant of symptoms and abnormal physiology in even mild asthma. ICS reduce inflammation and improve symptoms, lung function, morbidity, and mortality in chronic persistent asthma of varying severity. The effectiveness of early intervention in mild persistent asthma (recent onset) had not been established. This study aimed to evaluate the merits of early intervention.

Methods

Patients: 7,241 patients at 499 centres in 32 countries.

Inclusion criteria:

- Mild asthma with symptoms \geq once weekly and $<$ daily;
- Reversible airflow obstruction; post-bronchodilator increase in forced expiratory volume in 1s (FEV_1) $>12\%$ or PEF variation of $>15\%$ on two occasions over 2wk.

Exclusion criteria:

- Asthma $>2y$ or $>30d$ previous steroid treatment;
- Predicted FEV_1 : $<60\%$ (pre-) or $<80\%$ (post-bronchodilator).

Groups:

- Inhaled budesonide (400 micrograms od) from a Turbohaler for 3y ($n = 3597$), including 1,000 children ($<11y$) who had 200 micrograms od;
- Inhaled placebo ($n = 3568$), including 974 children ($<11y$).

Primary endpoint: Time to first severe asthma-related event, defined as hospital admission, emergency treatment (systemic steroids and nebulized/parenteral bronchodilators), or death.

Secondary endpoints:

- Asthma symptoms, asthma-free days, life restriction in previous 2wk;
- Time to introduction of inhaled or oral steroid treatment;
- Spirometry; pre- and post-bronchodilator FEV₁;
- Adverse events.

Follow-up: At 6 and 12wk; then every 3mo for 3y.

Results

Table 17.2 Summary of results

| Primary endpoint | Budesonide (n = 3,597) | Placebo (n = 3,568) | p |
|---|---------------------------|------------------------|---------|
| Risk of first severe asthma-related event at 3y | 117 (3.5%) | 198 (6.5%) | <0.0001 |
| Secondary endpoints | | | |
| Symptom-free days | 93% | 90% | <0.0001 |
| ICS or oral steroids by 3y | 1121 (31%) | 1599 (45%) | <0.0001 |
| Requiring at least one course of prednisolone | 547 (15%) | 825 (23%) | <0.0001 |
| Change in pre-bronchodilator FEV ₁ at 3y (% predicted) | +3.49 | +1.77 | <0.0001 |

Discussion

This study showed substantial morbidity with mild asthma in the first few years after diagnosis. Early intervention with once-daily budesonide reduced the risk of a severe asthma exacerbation by nearly 50%, and the risk of a life-threatening attack by >60%. Effectiveness was independent of all baseline characteristics, including lung function and treatment. Delayed introduction of inhaled steroids may reduce benefit. (See Table 17.2.)

Problems

- Budesonide effects likely reduced by allowing patients to start ICS anytime to reduce dropouts (29% on placebo and 27% on budesonide) and differential withdrawal. About 50% of the placebo group had steroids at some stage, and about 30% took ICS in the first year.
- Post-bronchodilator FEV₁ in adolescents not improved by budesonide, though there was less reduction over time, compared to placebo. Not seen in other studies, but may be that loss of lung function occurs early after diagnosis of asthma. Adherence to treatment may also have an effect.
- Most frequent adverse effects (>5% patients) were similar: respiratory infections, rhinitis, pharyngitis, bronchitis, sinusitis, conjunctivitis, headache, fever, and accidental injury. Eleven died (three budesonide, eight placebo); only one case asthma-related.
- Growth rate in 5–15y children on budesonide reduced by –0.43cm/y (CI –0.54 to –0.32), compared with placebo. No difference between 200 micrograms (<11y) and 400 micrograms doses. Effect greater during first 2y, amounting to 1.3cm at 3y. No later measurements made. Other studies suggest no effect on final height.

Asthma: long-acting β_2 agonist and inhaled steroid

Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid.

AUTHORS: Greening A, Ind P, Northfield M et al. (on behalf of Allen & Hanburys Ltd. UK Study Group).

REFERENCE: *Lancet* (1994) **344**, 219–24.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Addition of salmeterol to a standard dose of beclomethasone improves lung function and asthma control more rapidly and effectively than increasing the dose of ICS.

Impact

First study of an alternative strategy for asthma management, and the forerunner of many others, examining differing severities of asthma and baseline ICS doses. Adding a long-acting β_2 agonist (LABA), instead of increasing the ICS dose, has been adopted in national and international guidelines.

Aims

The recognition of underlying airway inflammation in even mild asthma encouraged early use of ICS. Guidelines previously recommended doubling the ICS dose in uncontrolled asthma. However, there is little controlled evidence regarding stepwise increases in ICS. This study aimed to compare two strategies—increasing the ICS dose or addition of salmeterol (a LABA) in adult patients with asthma suboptimally controlled on BDP 400 micrograms od.

Methods

Patients: 426 patients at 99 GP centres in the UK.

Inclusion criteria: Adult patients with asthma:

- Taking BDP by metered dose inhaler (MDI) (200 micrograms bd);
- Symptomatic on ≥ 4 d out of last 7 d during 2wk run-in;
- Variation in PEF of $\geq 15\%$ over 1wk.

Exclusion criteria: No prednisolone (past 6wk) and ≤ 4 courses (past 1y).

Groups: Patients matched for age, gender, morning (a.m.) and evening (p.m.) PEF, and asthma exacerbations in the previous year:

- BDP (200 micrograms bd by MDI) and salmeterol (50 micrograms bd by diskhaler, DKH) ($n = 220$);
- BDP (500 micrograms bd by MDI) and placebo (by DKH) ($n = 206$).

Primary endpoint: Mean a.m. PEF as change from baseline.

Secondary endpoints:

- Mean p.m. PEF as change from baseline at wk 1;
- Proportion of symptom-free days and nights;
- Mean daily and nightly use of salbutamol relief.

Follow-up: Patients recorded medication use, a.m./p.m. PEF, asthma symptoms (scored 0–4 on diary card daily during second week of run-in and last week of each month), and were assessed at 1-, 3-, and 6-monthly visits.

Results**Table 17.3** Summary of results

| Primary endpoint (mean change in a.m. PEF) | Salmeterol + BDP 200 micrograms bd (n = 220) | BDP 500 micrograms bd (n = 206) | p |
|--|--|---------------------------------------|--------|
| At wk 1 | 20L/min | 3L/min | <0.001 |
| At wk 21 | 28L/min | 6L/min | <0.01 |
| Secondary endpoints | | | |
| Mean change in p.m. PEF from baseline at wk 1 | +15L/min | –5L/min | <0.01 |
| Symptom-free days at wk 21 | 44% | 39% | ns |
| Daytime relief salbutamol use (puffs/d) at wk 21 | 2.1 | 2.4 | ns |

Baseline: mean age = 48y; mean a.m. PEF = 349L/min (74% predicted).

Discussion

Addition of salmeterol to patients symptomatic on BDP 400 micrograms/d was significantly better than increasing the BDP dose 2-fold, with a.m. and p.m. PEF at wk 1 maintained throughout the period of study. Favourable responses were commoner with salmeterol than increasing the BDP dose. Salmeterol also rapidly improved symptom control, reduced rescue salbutamol use (statistically significant at certain time points), and produced no increase in exacerbations of asthma. In stable persistent asthma, addition of formoterol (another LABA) to steroid (budesonide) improves symptoms and lung function, and reduces the rate of severe exacerbations, more than increasing the steroid dose alone (FACET: *N Engl J Med* (1997) **337**, 1405–11). (See Table 17.3.)

Problems

- Salmeterol might be expected to produce greater bronchodilatation than an increase in ICS dosage; however, the 6mo study should have allowed time for improved airway calibre with anti-inflammatory therapy.
- A total of 136 withdrawals (32%), reflecting the unrestricted ‘real-world’ design, equally distributed between the groups.
- Response to increasing BDP dose was disappointing; p.m. PEF unchanged over 21wk (a.m. PEF did increase). No suggestion of differential non-compliance (both groups recorded >90% for DKH and MDI), and study was double-dummy (all given treatment or placebo at some stage) and double-blinded.
- Adverse effects were predictable, with both treatments well tolerated.

Asthma: leukotriene receptor antagonists

Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma.

AUTHORS: Reiss T, Chervinsky P, Dockhorn R et al.

REFERENCE: *Arch Intern Med* (1998) **158**, 1213–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Montelukast improves asthma control and is generally well tolerated.

Impact

Montelukast, an oral leukotriene receptor antagonist, has an additive role in the management of chronic asthma.

Aims

Cysteinyl leukotrienes are involved in the pathogenesis of asthma. Montelukast is a potent, specific, once-daily leukotriene receptor antagonist. This trial was designed to assess the efficacy and tolerability of oral montelukast in patients with asthma.

Methods

Patients: 681 patients randomized (607 patients completed 12wk study) at 50 centres in the USA.

Inclusion criteria: Non-smokers with:

- Intermittent or persistent stable asthma for >1y;
- FEV₁ 50–85% predicted at baseline;
- ≥15% increase in FEV₁ post-salbutamol;
- 2wk asthma daytime symptom score >64 (out of 336);
- Daily average use of ≥1 puff of salbutamol.

Groups: Groups matched for age, gender, race, asthma duration, ICS usage (23%), FEV₁, PEF, daytime and nocturnal symptoms, and rescue salbutamol use:

- Oral montelukast (10mg nocte) (*n* = 408);
- Placebo (*n* = 273).

Primary endpoint: FEV₁, daytime asthma symptom score.

Secondary endpoints:

- Morning and evening PEF;
- Daily salbutamol use;
- Nocturnal awakenings/wk;
- Asthma-specific QoL;
- Change in peripheral blood eosinophil count;
- Asthma control.

Follow-up: Study duration 12wk.

Results

Table 17.4 Summary of results

| Primary endpoint | Placebo (n = 273) | Montelukast 10mg (n = 408) | p |
|---|----------------------|-------------------------------|--------|
| Change in FEV ₁ at 12wk | +4.2% | +13.1% | <0.001 |
| Secondary endpoints | | | |
| Change in morning PEF | +4.6L/min | +24.0L/min | <0.001 |
| Change in evening PEF | +4.2L/min | +15.9L/min | <0.001 |
| Nocturnal awakenings/wk | -0.80 | -1.66 | <0.001 |
| Peripheral eosinophils × 10 ⁹ /L | -0.03 | -0.092 | <0.001 |

Baseline: median age = 31y; 55% = ♀; 94% had exercise-induced asthma; 90% had allergic rhinitis; 23% used ICS. Baseline FEV₁ = 2.5L (67% predicted).

Discussion

Montelukast provided clinical benefit, with significant improvement in all asthma control variables, compared with placebo, maintained over 12wk. Near maximal benefit occurred on the first day of treatment. There was no evidence of rebound deterioration on discontinuation of treatment. An electronic, centralized spirometry system provided quality control, thus ensuring accuracy. Treatment was discontinued, because of adverse effects in 12 patients on placebo (4.4%) and nine on montelukast (2.2%). Increased alanine transaminase (ALT) occurred in 2.5% patients on montelukast and in 1.5% on placebo (ns). (See Table 17.4.)

Problems

- Benefits were relatively modest in this group of patients with quite severe chronic asthma (baseline FEV₁ 67% predicted) but were similar in patients taking ICS (dose not specified) and those not on ICS.
- This study did not compare montelukast with more conventional treatment regimes. Subsequent studies have shown improved control when montelukast is added to ICS, compared to ICS monotherapy (*Thorax* (2003) 58, 204–10), but there is greater benefit from the addition of a LABA in the medium term. The SE profile of montelukast may be considered more favourable than a LABA.
- Montelukast reduced prednisolone courses (6.9%), compared with placebo (9.6%), but this was not significant. Further studies of the steroid-sparing effect of montelukast are required.
- This was a short-term study of only 12wk duration; longer studies are required to assess chronic changes.

Chronic obstructive pulmonary disease: pulmonary rehabilitation

Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation.

AUTHORS: Griffiths T, Burr M, Campbell I *et al.*

REFERENCE: *Lancet* (2000) 355, 362–8.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

An intensive multidisciplinary outpatient rehabilitation programme is an effective short- and long-term intervention in patients with severe COPD and has the potential to reduce the use of health services.

Impact

Pulmonary rehabilitation is now standard for patients with severe COPD, recommended by the UK's British Thoracic Society and NICE.

Aims

Pulmonary rehabilitation had been suggested as beneficial in the short term in controlled trials of patients with COPD. This study aimed to evaluate both short- and long-term benefits, particularly with regard to health status and health service usage, as well as the walking distance.

Methods

Patients: 200 patients from multiple hospital consultants and GPs in the UK.

Inclusion criteria: Referred for pulmonary rehabilitation with:

- Chronic disabling lung disease, clinically stable over 2mo;
- FEV₁ <60% predicted, with <20% bronchodilator reversibility.

Exclusion criteria:

- Unable to walk;
- Severe sensory or cognitive impairment;
- Symptomatic ischaemic heart disease.

Groups: Stratified by gender and obstructive lung disease (>97%):

- Multidisciplinary pulmonary rehabilitation: over 3 half-days (2h sessions) per wk, for 6wk (*n* = 99);
- Usual outpatient or 1° care F/U over 12mo (*n* = 101).

Primary endpoints: Hospital admissions, days in hospital with respiratory and non-respiratory illness.

Secondary endpoints:

- GP consultations, home visits, contacts with 1° care staff;
- Walking ability: 10m shuttle walk test;
- Generic health status: SF36 questionnaire, hospital anxiety and depression (HAD) score;
- Disease-specific health status: St George's Respiratory Questionnaire (SGRQ), chronic respiratory disease questionnaire (CRDQ).

Results

Table 17.5 Summary of results

| Primary endpoints | Pulmonary rehab (n = 99) | Usual treatment (n = 101) | p |
|-------------------------------------|--------------------------|---------------------------|-------|
| Patients admitted to hospital | 40 (40%) | 41 (41%) | ns |
| Hospital admissions/patient | 1.4 | 1.9 | 0.04 |
| Resp. illness mean days in hospital | 9.4 | 18.1 | 0.02 |
| Secondary endpoints | | | |
| GP consultations resp. illness | 4.7 | 4.5 | 0.21 |
| GP consults all cause | 8.6 | 7.3 | 0.03 |
| Resp. 1° care home visits | 1.3 | 1.8 | 0.34 |
| All cause 1° care home visits | 1.5 | 2.8 | 0.04 |
| Walking distance (m) at 1y | 148 | 113 | 0.002 |

Baseline: mean age = 68y; mean FEV₁ = 0.9L (39% predicted); mean transfer coefficient (KCO) = 81% predicted.

Discussion

Pulmonary rehabilitation did not affect the numbers admitted to hospital but did reduce admissions per patient and days spent in hospital (whether for respiratory illness or all causes) by about 50%. Although the number of consultations in GP (for all causes) increased in the pulmonary rehabilitation group, home visits were reduced. The multidisciplinary rehabilitation programme produced large health improvements in disease-specific and general questionnaires, as well as the walking distance; statistically and clinically significant differences were persistent, if diminished at 1y. (See Table 17.5.)

Problems

- The programme had many components; the contribution of each is unclear. One aim was to change behaviour and attitude to chronic disability and handicap, which may have occurred through a general increase in fitness. This could also explain fewer 1° care attendances.
- The programme did not include a clinical psychologist, who might have increased the 'emotionally based' benefits (anxiety component of HAD and CRDQ), which appeared less robust than the physical measures.
- Together with more efficient use of 1° care services, there are potential cost savings. Economic analysis is needed.
- Treatment effects waned over the 1y F/U; unclear whether due to disease progression, exacerbations causing deconditioning, or failure to continue home exercise. Only 25% attended patient-led post-rehabilitation support sessions.
- A total of 138 of 338 referred did not fit the entry criteria or refused to participate.

Chronic obstructive pulmonary disease: long-acting anticholinergic

Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium.

AUTHORS: Vincken W, van Noord J, Greefhorst A *et al.* (on behalf of the Dutch/Belgian Tiotropium Study Group).

REFERENCE: *Eur Resp J* (2002) **19**, 209–16.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Tiotropium once daily is superior to multi-dosed ipratropium in improving dyspnoea and health-related quality of life (HRQOL), reducing exacerbations, and producing long-lasting bronchodilatation in patients with COPD.

Impact

Tiotropium should replace ipratropium in severe COPD. Fewer exacerbations and hospital admissions are economically beneficial. The long-acting bronchodilators salmeterol and formoterol are alternatives for those with ≥ 2 exacerbations per year.

Aims

Inhaled anticholinergics are effective bronchodilators, acting by reversing the increased cholinergic airway tone in COPD. Ipratropium had long been used in COPD, but tiotropium had several advantages, including longer duration of action and lack of taste. This study aimed to compare tiotropium with standard ipratropium, evaluating dyspnoea, exacerbations, HRQOL, and lung function.

Methods

Patients: 535 patients at 29 centres in the Netherlands and Belgium.

Inclusion criteria: COPD with:

- Age ≥ 40 y and $FEV_1 \leq 65\%$ predicted, and FEV_1/FVC ratio of $\leq 70\%$;
- Smoking history of >10 pack years (i.e. 20 cigarettes/d for 10y).

Exclusion criteria:

- Asthma, atopy, allergic rhinitis, or raised total blood eosinophil count;
- On regular O_2 therapy or recent URTI.

Groups: Double-blind and double-dummy. Matched for age, sex, concomitant inhaled β_2 agonist/steroid, theophylline, and prednisolone (<10 mg/d) usage:

- Tiotropium (18 micrograms od dry powder capsule via Handihaler) ($n = 356$);
- Ipratropium (40 micrograms qds [two puffs of 20 micrograms] MDI) ($n = 179$).

Primary endpoint: Trough FEV_1 and FVC (defined as mean FEV_1 and FVC on subsequent clinic visits, 23–24h after last tiotropium dose or 8–9h after last ipratropium dose).

Secondary endpoints:

- Breathlessness: transition dyspnoea index (TDI). Focal score ≥ 1 unit considered clinically meaningful;
- HRQOL using SGRQ and SF36. Increase in SGRQ ≥ 4 units considered clinically meaningful;
- Exacerbation rate and safety.

Follow-up: At 1, 7, 13, 26, 39, and 52wk.

Results

Table 17.6 Summary of results

| Primary endpoint | Tiotropium od (n = 302) | Ipratropium qds (n = 141) | p |
|--|----------------------------|------------------------------|--------|
| Trough FEV ₁ change (1y) | +120mL | -30mL | <0.001 |
| Trough FVC change (1y) | +320mL | +110mL | <0.05 |
| Secondary endpoints | | | |
| Change in TDI (1y) | +0.46 | -0.441 | <0.05 |
| Change in SGRQ (1y) | -3.74 | -0.44 | 0.004 |
| % having ≥ 1 exacerbation over 1y | 35% | 46% | 0.01 |
| Number of exacerbations/patient/y | 0.73 | 0.96 | 0.006 |

Baseline: 85% = σ^2 ; mean age = 64y; mean FEV₁ = 1.23L (41% predicted); mean FEV₁/FVC ratio = 46%.

Discussion

This paper summarized the results of two studies (of identical design), one of which extended a previous study. Tiotropium more significantly improved lung function and reduced rescue salbutamol usage and dyspnoea. Lung function improved more significantly, and rescue salbutamol usage and dyspnoea were reduced more significantly by tiotropium. Furthermore, more patients achieved clinically meaningful improvement in HRQOL. Exacerbation rates and duration, hospital admissions and duration, and time to admission were also reduced further by tiotropium, with potentially beneficial economic implications. (See Table 17.6.)

Problems

- Tiotropium and ipratropium doses may not have been equivalent; for 1h after the first dose, FEV₁ was marginally (non-significantly) higher after ipratropium. 'Non-bronchodilator' effects may have different dose-response; ipratropium 80 micrograms qds may be a better comparator.
- Tiotropium caused significantly more dry mouth (12.1%) than ipratropium (6.1%, $p = 0.03$), suggesting greater anticholinergic efficacy.
- A total of 92 patients were withdrawn from the study; adverse effects, including worsening of COPD in 10.1% on tiotropium and 12.8% on ipratropium.
- Mechanism behind exacerbation reduction remains unclear; possible that sustained bronchodilatation raises thresholds of symptom awareness.
- Compliance, which might favour the once-daily medication, was not assessed.

Chronic obstructive pulmonary disease: inhaled steroids and long-acting β_2 agonists

TORCH (Towards a Revolution in COPD Health) study: Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease.

AUTHORS: Calverley P, Anderson J, Celli B et al.

REFERENCE: *N Engl J Med* (2007) 356, 775–89.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In COPD, there are significant benefits from single inhaler combination therapy of an inhaled steroid and a LABA, over either alone. However, mortality at 3y is not significantly reduced.

Impact

Combination therapy, with an inhaled steroid and a LABA in a single inhaler, is recommended for the treatment of moderate to severe COPD. Evidence is provided for the CV safety of salmeterol alone. Inhaled steroid monotherapy in COPD cannot be recommended, though further study is warranted.

Aims

The UK's NICE recommends the use of an inhaled steroid for those patients with COPD and $FEV_1 < 50\%$ predicted, with ≥ 2 exacerbations per year. This trial aimed to investigate the effects of a LABA, inhaled steroid, and combination on overall mortality over 3y.

Methods

Patients: 6,184 patients at 444 centres in 42 countries.

Inclusion criteria:

- Age 40–80y with at least 10 pack years of smoking history;
- Pre-bronchodilator $FEV_1 < 60\%$ predicted;
- $FEV_1/FVC \leq 70\%$;
- $< 10\%$ increase in predicted FEV_1 with salbutamol 400 micrograms.

Groups: Matched for age, sex, BMI, geographic location, smoking status, previous treatment, prior exacerbation rate, FEV_1 , and SGRQ score:

- Salmeterol plus fluticasone (50 micrograms/500 micrograms bd) ($n = 1,533$);
- Fluticasone (500 micrograms bd) ($n = 1,534$);
- Salmeterol (50 micrograms bd) ($n = 1,521$);
- Placebo ($n = 1,524$).

Primary endpoint: Time to death from any cause at 3y, regardless of whether the patients continued to take study medication.

Secondary endpoints:

- Frequency of exacerbations;
- Health status according to the SGRQ;
- Post-bronchodilator FEV_1 .

Follow-up: All patients were assessed every 3mo.

Results**Table 17.7** Summary of results

| Primary endpoint | Placebo | Combination salmeterol and fluticasone | <i>p</i> |
|--|-------------|--|----------|
| No. of deaths from any cause | 231 (15.2%) | 193 (12.6%) | 0.05 |
| Secondary endpoints | | | |
| Annual exacerbation rate | 1.13 | 0.85 | <0.001 |
| SGRQ change from baseline | +0.2 units | −3.0 units | <0.001 |
| Mean change in FEV_1 over 3y | −0.062L | +0.029L | <0.001 |
| Baseline: mean FEV_1 in all groups was 1.1L (44% predicted). | | | |

Discussion

The study provided excellent epidemiological data, showing 35% of deaths in patients with COPD were due to pulmonary causes, 27% to CV disease, and 21% to cancer. The combination of salmeterol and fluticasone did not meet the predefined criteria for improved survival but did demonstrate significant improvement in exacerbation rates, health status, and lung function over placebo, fluticasone, and salmeterol alone. Salmeterol alone offered similar advantages over placebo, with no excess of CV events. (See Table 17.7.)

Problems

- Failure to achieve significant reduction in mortality with combination treatment may be due to lower than expected mortality on placebo; study powered to detect 25% reduction in mortality at 3y.
- High number of dropouts (~40%, greatest on placebo) likely to underestimate benefit from the active drugs.
- Although patients with moderate to severe disease were included, potential recruitment to placebo may have mitigated against more severe cases, particularly those with frequent exacerbations.
- The study showed an expected increase in oropharyngeal SEs, but no difference in fractures or cataracts; 3y may be insufficient to detect significant differences.
- Significant excess of patients with pneumonia in the groups that received fluticasone, either alone or in combination. A subsequent Cochrane review confirmed ICS use in COPD increases the risk of serious adverse pneumonia events but does not increase mortality (*Cochrane Database Syst Rev* (2014) 3, CD010115).

Chronic obstructive pulmonary disease: long-term oxygen therapy

Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party.

AUTHORS: Stuart-Harris C, Bishop J, Clark T et al.

REFERENCE: *Lancet* (1981) 1, 681–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In hypoxaemic cor pulmonale due to severe COPD, O₂ therapy (for at least 15h/d) prolongs life. However, this effect is not seen until after 500d of treatment in ♂ patients.

Impact

First RCT of long-term O₂ therapy (LTOT) in cor pulmonale due to severe COPD, and the first to show a reduction in mortality from a treatment other than smoking cessation. It was the foundation study for all guidelines on the use of LTOT.

Aims

Severe COPD complicated by hypoxic cor pulmonale and carbon dioxide (CO₂) retention carries a grave prognosis. Correction of hypoxaemia can reverse pulmonary HTN and 2° polycythaemia. This study aimed to examine O₂ therapy for 15h/d over 3y to determine whether it could reduce mortality and improve exercise tolerance and working capacity.

Methods

Patients: 87 patients at three centres in the UK.

Inclusion criteria:

- Age <70y;
- Irreversible airflow obstruction with chronic bronchitis or emphysema;
- FEV₁ <1.2L;
- P_aO₂ 5.33–8.0kPa (breathing air at rest), clinically stable over 3wk;
- ≥1 episode of heart failure with ankle oedema.

Exclusion criteria: Restrictive lung disease, severe HTN, proven CHD.

Groups: Matched for age, P_aO₂, P_aCO₂, pulmonary artery pressure (PAP), cardiac output, and red cell mass (RCM):

- LTOT: At least 15h/d, 2L/min via nasal prongs (*n* = 42; 33 men and 9 women);
- Standard therapy (chosen by physician): Included diuretics, bronchodilators, digoxin, antibiotics, and prednisolone (*n* = 45; 33 men and 12 women).

Primary endpoint: Survival up to 5y.

Secondary endpoints: ABGs (arterial blood gases), annual RCM (using $^{51}\text{chromium}$ -tagged red cells), annual PAP (right heart catheter).

Follow-up: Clinic review every 2mo for 3y. Occasional home visits.

Results

Table 17.8 Summary of results

| Primary endpoint | LTOT ($n = 42$) | Standard therapy ($n = 45$) | p |
|---|-------------------|-------------------------------|-------|
| Deaths up to 5y | 19 (45%) | 30 (67%) | <0.05 |
| Secondary endpoints | ($n = 22$) | ($n = 18$) | |
| P_aO_2 on air fall in mmHg/y in survivors >500d | +0.11 | -0.96 | <0.05 |
| P_aCO_2 on air increase in mmHg/y in survivors >500d | -0.96 | +1.2 | 0.05 |
| PAP on air (mmHg/y) ($n = 21$) | -0.06 | +2.79 | <0.05 |
| RCM (mL/kg/y) | -1.25 | +0.12 | <0.05 |
| Baseline means: age = 57y; $FEV_1 = 0.68\text{L}$; $P_aO_2 = 6.7\text{kPa}$; $P_aCO_2 = 7.23\text{kPa}$. | | | |

Discussion

O_2 for 15h overnight produced significant survival benefits. Benefit was only seen in men after 500d, when a linear risk of dying of 29% per annum in controls was significantly reduced to 12% by LTOT ($p = 0.04$). Surprisingly, PAP was not reduced by O_2 therapy. Risk of early death was predicted by ♀ gender, high initial RCM, and raised P_aCO_2 . In these patients, there was a fall in P_aO_2 and a rise in P_aCO_2 over time, with O_2 failing to prevent disease progression. Patients with high P_aCO_2 or mood disturbance who survived long-term benefited the most from LTOT. (See Table 17.8.)

Problems

- Not placebo-controlled, and O_2 provided as concentrator, liquid O_2 , or cylinders by different centres. Compliance unproven, though treatment proved generally acceptable, with only one withdrawal. Cylinder weighing, time records, and home visits suggested O_2 usage was at least 15h/d.
- Despite similar physiology, women died more rapidly (in a linear fashion). This was not due to more severe disease and remains unexplained. Mortality in men followed an unusual pattern, with no divergence between treated and untreated patients until 500d. A likely explanation is that severely ill patients (too advanced to obtain benefit) were included, and it was not until they died that benefit in the remainder was observed.
- No information on longer O_2 usage (>15h/d). NOTT US study showed greater benefit from O_2 over 24h vs night only (12h) in severe COPD (hypoxaemia and pulmonary HTN), but no CO_2 retention.
- No reduction in admissions or improved work record seen with LTOT, but many patients elderly and/or disabled. No cost/benefit analysis undertaken.
- Improved well-being reported in some on O_2 , but not formally quantified. Although QoL and exercise capacity are now central to such trials, measurement tools were not available when planning this study.

Chronic obstructive pulmonary disease: non-invasive ventilation

Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards.

AUTHORS: Plant P, Owen J, Elliott M.

REFERENCE: *Lancet* (2000) 355, 1931–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Compared with standard therapy, NIV leads to more rapid improvement and reduces mortality in exacerbations of COPD when used in a general ward setting for patients with mild to moderate acidosis. It also reduces the need for invasive ventilation.

Impact

Recommended by the UK's British Thoracic Society for acidotic patients, NIV is considered standard therapy for acute exacerbations of COPD. It should be used in EDs and medical wards to reduce the need for intubation and intensive care.

Aims

Prospective RCTs of NIV in ICU settings had shown reductions in the need for intubation and in-hospital mortality in patients with acute exacerbations of COPD. Studies in non-ICU settings had produced mixed evidence. This study aimed to determine whether NIV was feasible in a ward (non-specialized) environment and whether it could reduce intubation and mortality, compared with standard treatment, in mild to moderate acute acidotic exacerbations of COPD.

Methods

Patients: 236 patients in general respiratory wards at 14 UK hospitals.

Inclusion criteria: Adults admitted as emergency with acute exacerbations of COPD (respiratory rate (RR) $>23/\text{min}$, pH 7.25–7.35, and $\text{PaCO}_2 >6\text{kPa}$ on ward arrival, and $<12\text{h}$ since admission).

Exclusion criteria: pH <7.25 ; GCS <8 ; pneumothorax.

Groups: ITT analysis:

- **Standard:** Controlled O_2 aiming for arterial O_2 saturation (SaO_2) 85–90%; nebulized salbutamol/terbutaline and ipratropium; prednisolone and antibiotic. Aminophylline and doxapram at discretion of attending clinician ($n = 118$);
- **NIV:** Standard treatment and nurse/physiotherapist initiated NIV via face/nasal mask with expiratory pressure $4\text{cmH}_2\text{O}$ and inspiratory pressure $10\text{cmH}_2\text{O}$, then 15–20 cmH_2O (or max. tolerated over 1h). O_2 to keep SaO_2 85–90%. NIV for: as long as possible (d 1); 16h (d 2); 12h (d 3); then discontinued routinely (d 4) ($n = 118$).

Primary outcome: 'Need for intubation' (defined by any of the following within 14d of admission: pH <7.20 ; pH 7.20–7.25 twice, 1h apart;

hypercapnic coma (GCS <8 and $\text{PaCO}_2 > 8\text{kPa}$); $\text{PaO}_2 < 6\text{kPa}$ despite max. tolerated O_2 ; cardiorespiratory arrest).

Secondary endpoints: RR, P_aO_2 and P_aCO_2 (at 1 and 4h; d 3; within 3mo of discharge). Also: mobility, nutrition, mask comfort, breathlessness, nursing workload.

Results

Table 17.9 Summary of results

| Primary endpoint | NIV | Standard | <i>p</i> |
|---|-------------------|-------------------|----------|
| Failed | 18 (15%) | 32 (27%) | 0.02 |
| Died | 12 (10%) | 24 (20%) | 0.05 |
| Secondary endpoints* | (<i>n</i> = 101) | (<i>n</i> = 106) | |
| Correction of acidosis at 1h | pH 7.342 | pH 7.324 | 0.02 |
| Median time to relief of breathlessness | 4d | 7d | 0.03 |

* pH and RR improved after 4h, but acidosis and breathlessness improved more rapidly with NIV. Baseline: mean FEV₁ = 26.7% predicted; mean TLCO = 28.4% predicted. Well-matched groups. Mean: RR = 28/min; pH = 7.32; PaCO_2 = 8.75kPa. Most (93%) tolerated NIV, which took an additional 26min of nursing time.

Table 17.10 Summary of results

| Subgroup | Outcome | NIV | Standard | <i>p</i> |
|----------|---------------------|-------------|-------------|----------|
| pH <7.30 | Need for intubation | 13/36 (36%) | 16/38 (42%) | 0.64 |
| | Died in hospital | 8/36 (22%) | 13/38 (34%) | 0.31 |
| pH ≥7.30 | Need for intubation | 5/82 (6%) | 16/80 (20%) | 0.01 |
| | Died in hospital | 4/82 (5%) | 11/80 (14%) | 0.06 |

Patients with pH <7.25 excluded, as poor prognosis without ventilation (randomization unethical).

Discussion

NIV was feasible on general wards. It produced more rapid correction of acidosis, greater fall in RR, and a trend towards more rapid correction of P_aCO_2 , suggesting it increased minute ventilation by increasing tidal volume; the RR reduction offloaded the respiratory muscles, leading to faster relief of breathlessness. 'Need for intubation' used as the primary endpoint to avoid confounding effects of ICU bed availability and different doctors' views about indications for intubation/ventilation. (See Tables 17.9 and 17.10.)

Problems

- Findings apply only to the use of a simple ventilator, standard protocol, and limited range of masks (four types) in wards staffed by nurses who received a mean 7.6h training (first 3mo) and 0.9h (per subsequent months).
- Not all tolerate NIV, due to discomfort from tight masks.
- Subgroup with pH <7.30 (*n* = 74) did not significantly benefit from NIV in terms of treatment failure or mortality, although the study was not powered for this analysis; more sophisticated NIV, endotracheal intubation, or intensive care may be needed in this group.
- Physiological changes due to NIV appear small (no difference between groups at 4h). However, this, in part, reflected the removal of data for 'treatment failures' (commoner in the standard group).

Severe emphysema: lung volume reduction surgery

NETT (National Emphysema Treatment Trial): A randomized trial comparing lung-volume reduction surgery with medical therapy for severe emphysema.

AUTHORS: NETT research group.

REFERENCE: *N Engl J Med* (2003) **348**, 2059–73.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Lung volume reduction surgery (LVRS) improves exercise capacity, but not survival, compared with maximal medical therapy, in selected patients.

Impact

The UK's NICE recommends consideration of LVRS for breathless patients with marked restriction of activities despite maximal medical therapy and $FEV_1 > 20\%$, $P_aCO_2 < 7.3$, diffusion capacity (TLCO) $> 20\%$, and predominantly upper lobe emphysema.

Aims

Prior to this trial, LVRS was proposed as a palliative treatment for emphysema. This study aimed to investigate the effect of LVRS on mortality, and the magnitude and durability of improvement in breathlessness, and to identify patient selection criteria.

Methods

Patients: 1,218 patients from 17 clinics in the USA.

Inclusion criteria:

- Evidence of emphysema on history, examination, and CT scan;
- Pre-rehabilitation $FEV_1 \leq 45\%$, total lung capacity (TLC) $\geq 100\%$, residual volume (RV) $\geq 150\%$ predicted, $PaO_2 \geq 6kPa$, $PaCO_2 \leq 8kPa$;
- Non-smoker for at least 4mo before and during the study;
- BMI $< 32.3kg/m^2$; non-smoker for $> 4mo$ before/during study;
- Approval by thoracic surgeon, and cardiac and respiratory physician for surgery;
- Completion of rehabilitation programme.

Exclusion criteria:

- Post-rehabilitation $FEV_1 \leq 20\%$, and either TLCO $\leq 20\%$ or non-heterogenous emphysema on CT scan;
- Bronchiectasis, previous LVRS, lobectomy, sternotomy, or giant bullae;
- Pulmonary HTN, unexplained weight loss, daily use of 20mg of prednisolone (or greater), or cardiac arrhythmia;
- 6min walking distance (6MWD) $\leq 140m$ post-rehabilitation.

Groups: Matched for age, race, distribution of emphysema, and 6MWD:

- LVRS: bilateral, stapled, wedge resection of 20–35% of each lung by video-assisted thoracoscopic surgery or median sternotomy ($n = 608$);
- Maximal medical therapy only ($n = 610$).

Primary endpoint: Mortality and maximal exercise capacity after 2y (on cycle ergometry).

Secondary endpoints:

- Pulmonary function tests;
- 6MWD;
- Results on SGRQ, Quality of Well-Being Scale, and a Shortness of Breath Questionnaire.

Follow-up: At 6mo, 1y, and annually thereafter.

Results

Table 17.11 Summary of results

| Primary endpoints (no. of deaths/total) | LVRs | Medical | <i>p</i> |
|--|---------------|---------------|----------|
| Overall mortality | 157/608 (26%) | 160/610 (26%) | 0.9 |
| Upper lobe emphysema and low exercise capacity | 26/139 (19%) | 51/151 (34%) | 0.005 |
| Secondary endpoints (no./total) | | | |
| Improvement in FEV ₁ | 134/313 (43%) | 62/330 (19%) | <0.001 |
| Improvement in exercise capacity at 24mo | 54/371 (15%) | 10/378 (2.6%) | <0.001 |
| Improvement in HRQOL | 121/371 (33%) | 34/378 (9%) | <0.001 |

Baseline: mean FEV₁ = 26.7% predicted; mean TLCO = 28.4% predicted.

Discussion

LVRs was associated with greater improvement in lung function, exercise capacity, QoL, and dyspnoea than medical therapy. Surgery can reduce the risk of death among patients with upper lobe emphysema and low exercise capacity, with improvement in exercise capacity and QoL, but could increase mortality in other groups. (See Table 17.11.)

Problems

- After exclusion of 140 at high risk of death from surgery (according to interim analysis), the 538 randomized to surgery were more likely than the 540 randomized to medical therapy to have improvements in exercise capacity and QoL; however, there was no reduction in mortality over an average of 29mo F/U.
- The 90d mortality greater in the surgical group. No reduction in mortality seen at 90d, even in upper lobe emphysema and low exercise capacity.
- Significant finding of late mortality reduction following surgery in patients with low exercise capacity and upper lobe emphysema was demonstrated by subgroup analysis. Confirmatory prospective studies using these results as entry criteria are required.
- Unilateral LVRs may yield similar improvement with less mortality to bilateral LVRs, warranting further investigation.
- Ongoing research into bronchoscopic volume reduction (e.g. endobronchial valves)

Treatments for smoking cessation

A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation.

AUTHORS: Jorenby D, Leischow S, Nides M et al.

REFERENCE: *N Engl J Med* (1999) **340**, 685–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Treatment with bupropion significantly improves rates of smoking cessation, compared to nicotine patches or placebo. Combination of bupropion and a patch is not significantly more effective.

Impact

One of the first studies to confirm the benefit of bupropion in smoking cessation and compare it with nicotine replacement therapy (NRT). Bupropion plays an important part in cessation programmes.

Aims

Only a small proportion of those who attempt to stop smoking are successful. Studies have shown NRT to boost the rate of smoking cessation by a factor of up to 2.6. With mood and affect known to play an important role in motivation to use nicotine, this study aimed to determine whether bupropion, an antidepressant, was useful in helping people to stop smoking.

Methods

Subjects: 893 subjects at four centres in the USA.

Inclusion criteria: Motivated to quit smoking:

- Age >18y and weight ≥ 45.4 kg;
- Smoking >15 cigarettes/d.

Exclusion criteria:

- Significant medical condition, as assessed by the study site physician;
- Current psychiatric disorder, including depression;
- Dependence upon any other drug within the previous year.

Groups: All subjects received brief counselling and weekly assessments.

- Bupropion: 150mg sustained-release (Zyban®) for 9wk ($n = 244$);
- Nicotine patch: 21mg (7wk), 14mg (1wk), 7mg (1wk) ($n = 244$);
- Bupropion plus nicotine patch: for 9wk ($n = 245$);
- Matched placebo tablets and patches ($n = 160$).

Primary endpoints: Point prevalence abstinence rate at 6 and 12mo, judged by history and expired carbon monoxide concentration of ≤ 10 ppm. Continuous abstinence at all visits throughout the 12mo.

Secondary endpoints: Withdrawal symptoms, body weight, and BDI scores.

Follow-up: Assessments and relapse prevention counselling at 10, 12, 26, and 53wk. Counsellor also telephoned at 3, 4, 5, 7, and 11mo.

Results

Table 17.12 Summary of results

| Primary endpoints (at 12mo) | Placebo (n = 82) | Nicotine patch (n = 152) | Bupropion (n = 169) | p |
|--|---------------------|-----------------------------|------------------------|---------------------|
| Abstinent | 25 (15.6%) | 40 (16.4%) | 74 (30.3%) | <0.001 ⁺ |
| Continuously abstinent | 4 (5.6%) | 15 (9.8%) | 31 (18.4%) | <0.001 ⁺ |
| Secondary endpoints | | | | |
| Mean change withdrawal symptoms: d 14 | +0.76 | +0.52 | +0.55 | ns |
| Weight change: 7wk | +2.1kg | +1.6kg | +1.7kg | ns |

⁺ Nicotine patch vs placebo; ⁺ bupropion vs nicotine patch. Baseline means: age = 44y; 53% ♀; 93% Caucasian. Consumption = 27 cigarettes/d over 26y. Previous attempts to quit = 2.8.

- Bupropion adverse effects: 42.4% = insomnia (19.5% on placebo); 11.9% = discontinued (3.8% on placebo). Five serious adverse events (see Table 17.12.)

Discussion

Previous trials had shown people with negative affect were more likely to start smoking and to find it difficult to abstain. Bupropion resulted in higher rates of abstinence at 1y, compared with placebo or nicotine patches. There were no significant differences between bupropion alone and bupropion–nicotine patch combination, and the UK's NICE does not recommend combination treatment. Improvements in smoking cessation were independent of depression and withdrawal scores, which were unaltered by NRT or bupropion. NICE recommends bupropion (or NRT) for smokers who have expressed a desire to quit and as part of an abstinence contingent treatment (ACT) in which the smoker makes a commitment to stop smoking on a particular target date. Further investigation of the efficacy of nicotine e-cigarettes, sales of which are rapidly growing, is required.

Problems

- All received counselling, in addition to medication. It would be useful to determine the effect of this alone, although considerable resources would be required to provide this service for all patients.
- Volunteers may not represent most smokers, despite the 20% dropout.
- Overall efficacy of bupropion was limited; more than two-thirds were still smoking at 1y. Important to know if the benefits translate into significant savings in costs and improved long-term endpoints.
- Did not assess smoking cessation in patients with proven smoking-related diseases, e.g. ischaemic heart disease or COPD, in whom it may be most beneficial and cost-effective.

Pulmonary embolism: post-operative prophylaxis

Prevention of fatal postoperative pulmonary embolism by low doses of heparin.

AUTHORS: Kakkar V, Corrigan T, Fossard D et al.

REFERENCE: *Lancet* (1975) 2, 45–51, *Lancet* (1977) 1, 567–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

SC heparin significantly reduces post-operative mortality from PE, as well as the incidence and extent of DVT, without a significant rise in haemorrhagic risk.

Impact

Thromboprophylaxis with UFH or, more recently, LMWH is now standard practice for all patients undergoing surgical procedures and for other clinical episodes associated with a high risk of VTE disease.

Aims

VTE disease was, and still is, the cause of significant morbidity and mortality. Before routine thromboprophylaxis was introduced, studies proposed a 20–30% incidence of DVT following general surgery, rising to 40–60% after orthopaedic surgery. PE was reported to occur in around 5–10% of cases, being fatal in 1–2%. Although there had been several good-quality trials showing low-dose SC heparin to be highly effective at reducing the incidence of post-operative DVT, these trials did not produce a widespread change in practice, since the impact of heparin on the incidence of PE was not defined, and concerns remained about the risk of haemorrhage. This study attempted to answer these questions.

Methods

Patients: 4,031 patients at 27 international centres.

Inclusion criteria:

- Age >40y;
- Elective major surgical procedures only (i.e. requiring general anaesthesia, lasting >30min, requiring inpatient post-operative stay >5d).

Exclusion criteria:

- In centres using radioactive fibrinogen test: Emergency procedures, and patients having procedures on thyroid, left breast, and lower limbs (other than hip surgery);
- Patients receiving anticoagulant therapy.

Groups: 440 patients excluded from analysis, leaving 4,031 patients:

- Control group: No specific thromboprophylaxis ($n = 2033$);
- Heparin group: 5,000 units of calcium heparin (2h preoperatively and every 8h thereafter, for 7d or until ambulant) ($n = 1998$).

Primary endpoint: Death from PE (as defined by presence of fresh emboli in the pulmonary trunk, main pulmonary artery, or in ≥ 2 lobar arteries at post-mortem (PM), where no other cause of death was found).

Secondary endpoints:

- Diagnosis of DVT/PE;
- Operative and post-operative haemorrhage.

Follow-up: Until discharge or death in hospital.

Results

Table 17.13 Summary of results

| Data from 1977 paper* | Post-op deaths | PM examinations | Deaths from PE (at PM) |
|-------------------------|----------------|-----------------|---------------------------------|
| Control ($n = 2,033$) | 94 (4.6%) | 66 (70.2%) | 15 (21% of PMs) (0.74% overall) |
| Heparin ($n = 1,998$) | 76 (3.8%) | 50 (65.7%) | 0 |
| p | Not reported | >0.7 | <0.001 |

* *Lancet* (1977) 1, 567–9.

Discussion

The data quoted above derive from the 1977 F/U study (which excluded unreliable data from one centre) with unaltered conclusions. PE was the commonest cause of death in the control group, followed by pneumonia and MI. There were no deaths from PE in the heparin group. However, of the patients who died of PE, two-thirds were diagnosed PM, reflecting the acute and potentially catastrophic nature of the condition. The incidence of DVT was also found to be significantly less in the heparin group, in keeping with results from other trials. However, there were significantly fewer cases of bilateral/extensive DVT in the heparin group. There was no increase in haemorrhage, Hb drop, or transfusion requirement, although more wound haematomas were noted. (See Table 17.13.)

Problems

- No randomization to compression stockings.
- The high-risk period for VTE persists for 4–6wk post-operatively, particularly after orthopaedic procedures. This paper might have underestimated the number of deaths from PE and the subsequent impact of heparin.

Pulmonary embolism: type of heparin

A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism.

AUTHORS: Simonneau G, Sors H, Charbonnier B et al.

REFERENCE: *N Engl J Med* (1997) **337**, 663–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Initial SC therapy with the LMWH tinzaparin is as effective and safe as IV UFH in symptomatic patients with acute PE.

Impact

LMWH is now considered standard therapy and recommended by the UK's British Thoracic Society for patients with PE who do not require thrombolysis or embolectomy.

Aims

The efficacy and safety of LMWH in the initial management of patients with DVT are established. This study was designed to determine whether SC LMWH (tinzaparin) was superior to continuous IV UFH in consecutive patients with symptomatic PE, with regard to efficacy and safety.

Methods

Patients: 612 patients at 57 centres in France, Belgium, and Switzerland.

Inclusion criteria: PE confirmed by: (1) positive angiography, (2) high probability ventilation–perfusion (VQ) scan, or (3) indeterminate VQ scan combined with DVT confirmed by venography or compression ultrasonography (USS).

Exclusion criteria:

- Massive PE requiring thrombolysis or embolectomy (judged by the attendant physician);
- Active bleeding or contraindications to anticoagulation;
- Received therapeutic anticoagulation for >24h before study entry;
- Life expectancy of <3mo, hepatic or renal failure, pregnancy.

Groups: Matched for age, gender, weight, predisposing factors, and DVT:

- LMWH: Tinzaparin (175IU/kg od SC) (*n* = 304);
- UFH: Heparin (50IU/kg bolus IV), then initial infusion rate of 500IU/kg/d, subsequently adjusted so that APTT ratio was 2–3 (*n* = 308).

Primary endpoints: Combined outcome event of death, recurrent VTE, or major bleeding within the first 8d and at d90.

Secondary endpoint: Change from d 1 to d 8 in % of detectable pulmonary vascular obstruction.

Follow-up: Oral anticoagulation begun between the first and third days of initial heparin therapy (both groups) and continued for at least 3mo, aiming for INR 2–3. Heparin continued until INR ≥ 2.0 on two measurements made 24h apart, at least 5d after commencing heparin treatment.

Results

Table 17.14 Summary of results

| Primary endpoints | UFH (n = 308) | LMWH (n = 304) | p |
|---|------------------|-------------------|----|
| Death, recurrent VTE, or bleeding at 8d | 9 (2.9%) | 9 (3%) | ns |
| Death, recurrent VTE, or bleeding at 90d | 22 (7.1%) | 18 (5.9%) | ns |
| Secondary endpoints | (n = 260) | (n = 258) | |
| % decrease in pulmonary vascular obstruction at d 8 | 9.09 \pm 13.9 | 18.4 \pm 13.5 | ns |
| % of patients with improvement in VQ scan | 81% | 80% | ns |
| Baseline: mean age = 67y; 45% = ♂; 72% had DVT; mean pulmonary vascular obstruction 8 47% on VQ scan. | | | |

Discussion

This study suggested that tinzaparin, an LMWH, can be used safely and effectively with a once-daily regime in the management of patients with acute PE who do not require thrombolysis or embolectomy. During 3mo F/U, there was a non-significant trend towards better outcomes with LMWH over UFH. The trial confirmed previous studies which validated the use of LMWH in DVT, and extended the role of LMWH into the management of PE. Given the simplicity of once-daily SC administration, LMWH is established as the treatment of choice for acute PE without haemodynamic instability. (See Table 17.14.)

Problems

- A total of 222 patients in the LMWH group and 201 in the UFH group received therapeutic doses of UFH before randomization (for <24h, allowing their inclusion in the study). This makes the validation of LMWH in the first 24h of acute PE less clear-cut.
- 52% of the initial 1,482 patients who met the enrolment criteria were excluded for a variety of reasons. However, only 15% of suitable patients then declined participation.
- The authors acknowledge that their selection criteria excluded patients who were at highest risk of death (232 requiring thrombolysis or inferior vena caval umbrella), recurrent VTE, and haemorrhage. In the initial 8d of treatment, the incidence of critical events was only 3%. This unexpectedly low event rate markedly reduced the power of the study to detect a significant difference between the two treatment groups.
- The study was not blinded, though the independent committee assessing the critical events was unaware of the treatment group.

Obstructive sleep apnoea: nasal continuous positive airway pressure

Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial.

AUTHORS: Jenkinson C, Davies R, Mullins R *et al.*

REFERENCE: *Lancet* (1999) 353, 2100–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Therapeutic nasal CPAP (nCPAP) improves daytime somnolence and health status in patients with obstructive sleep apnoea (OSA).

Impact

nCPAP is now established as standard therapy for symptomatic OSA and recommended by SIGN as first-line therapy for moderate to severe OSA.

Aims

OSA is caused by airway occlusion during sleep, 2° to pharyngeal collapse. Each episode is terminated by transient arousal, which restores pharyngeal muscle tone, re-opening the airway. Recurrent obstructive and arousal episodes lead to sleep disturbance and daytime somnolence. This study aimed to assess whether therapeutic nCPAP reduces daytime sleepiness and improves overall health status, in comparison with subtherapeutic nCPAP.

Methods

Patients: 172 patients referred to one sleep unit in the UK.

Inclusion criteria:

- Men aged 30–75y;
- Epworth Sleepiness Score ≥ 10 out of 24;
- Patients with OSA—defined as >10 episodes of desaturation/h ($>4\%$ fall in SaO_2) during a sleep study, with confirmation that these episodes were caused by pharyngeal collapse.

Exclusion criteria:

- Patients preferring alternative therapy (e.g. weight loss, tonsillectomy);
- Urgent CPAP required for respiratory failure;
- Patient about to lose their job due to sleepiness.

Groups: Groups matched for all baseline characteristics, e.g. SF36 score, Epworth Score, age, weight, BMI, neck size, SaO_2 dips:

- Subtherapeutic control group: Received nCPAP at about $1\text{cmH}_2\text{O}$ (using the lowest machine pressure with restricted flow) for 4wk ($n = 53$);
- Therapeutic autotitrated nCPAP ($n = 54$).

Primary endpoints: at 4wk:

- Epworth Sleepiness Score (0–24, with 24 most sleepy);
- Objective sleepiness, as judged by maintenance of wakefulness test (MWT): Patients asked to resist sleep, while semi-recumbent in a dark room, then instructed to tap in response to a dim light flashing every 3s. Sleep defined as a failure to tap for 21s. Patient then immediately woken up, and the mean time to sleep onset over 160 daytime min calculated;
- Energy and vitality, as measured by the SF36 questionnaire;
- Self-reported health status, as judged by the mental component of the SF36 questionnaire, a higher score representing better mental health.

Results

Table 17.15 Summary of results

| Primary endpoint | Subtherapeutic nCPAP (n = 53) | Therapeutic nCPAP (n = 54) | p |
|---|-------------------------------|----------------------------|---------|
| Change from baseline in Epworth Score | −2.0 | −8.5 | <0.0001 |
| MWT | +3.5min | +10.4min | 0.002 |
| Change in energy and vitality score on SF36 (score 0–100) | +17 | +37.6 | <0.0001 |
| Change in mental component of SF36 | +4.3 | +10.6 | <0.0001 |

Baseline: mean age = 49y; mean BMI = 35; mean nocturnal desaturation = 31 dips >4% SaO₂/h; mean Epworth score = 16.5.

Discussion

Prior to this study, trials attempting to establish the benefit of CPAP in OSA were insufficiently blinded or used a tablet as placebo in the control group. The inclusion of a subtherapeutic nCPAP control arm in a double-blind fashion demonstrated large improvements in sleepiness measures with therapeutic nCPAP that were significantly greater than with subtherapeutic control treatment. The trial also provided data on nCPAP usage—patients in the therapeutic group used a mean of 5.4h/night, use correlating with improved Epworth Score. (See Table 17.15.)

Problems

- The subtherapeutic nCPAP control group demonstrated some statistically significant improvements in Epworth Sleepiness Score and SF36 scores, implying a positive placebo effect or possible actual benefit, and an underestimation of the actual benefits of nCPAP. Reassuringly, patients were not worse on sham treatment.
- Longer-term studies with other outcomes and comparison of nCPAP with other treatment modalities, e.g. tonsillectomy and weight loss, would be useful. It is also unclear whether patients with lower Epworth Scores would benefit from nCPAP.
- It would be useful to know about co-morbidities in the groups (e.g. ischaemic heart disease, previous CVA, HTN) and whether these affect the response to CPAP.

Small cell lung cancer: radiotherapy

Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide.

AUTHORS: Turrisi A, Kyungmann K, Blum R et al.

REFERENCE: *N Engl J Med* (1999) **340**, 265–71.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

Given concurrently with chemotherapy, twice-daily thoracic radiotherapy improves survival, compared with a once-daily regime.

Impact

The addition of early concurrent radiotherapy to standard chemotherapy for treatment of limited-stage small cell lung cancer improves survival; a twice-daily regimen improves outcome still further. Whether this is due to an increase in the biological dose or the acceleration of treatment is under further evaluation.

Aims

Small cell lung cancers can be divided into two categories: limited (clinically confined to one side of the chest) and extensive. For small cell lung cancer contained within a radical radiotherapy portal (limited-stage small cell lung cancer), radiotherapy had been demonstrated to improve survival. This study aimed to define the optimal radiotherapy regimen.

Methods

Patients: 417 patients from multiple centres in the USA.

Inclusion criteria:

- Histologically confirmed small cell lung cancer;
- Confined to one hemithorax \pm ipsilateral supraclavicular fossa;
- Staging by CT or MRI of the chest, abdomen, and brain; bone scan; bilateral iliac crest bone marrow aspiration; and biopsy-limited stage disease;
- Adequate organ function.

Treatment:

- Four cycles of cisplatin 60mg/m² on d 1 + etoposide 120mg/m² on d 1–3;
- Radiotherapy dose 45Gy, starting with first-cycle chemotherapy with either:
 - Once-daily group: 1.8Gy daily in 25 fractions over 5wk (*n* = 206);
 - Twice-daily group: 1.5Gy in 30 fractions over 3wk (*n* = 211);
- Prophylactic cranial irradiation offered to patients with complete response (2.5Gy in ten fractions over 2wk).

Primary endpoint: Overall survival from date of trial entry to date of death.

Statistical analysis:

- Target enrolment 400 patients;
- 82% power to detect 15% improvement in 2y survival;
- Patients randomized according to performance status and weight loss in 6mo before trial entry.

Follow-up: Median F/U 8y.

Results

Table 17.16 Summary of results

| | Twice-daily group (n = 196) | Once-daily group (n = 185) | p |
|----------------------|--------------------------------|-------------------------------|--------------|
| Median survival | 23mo | 19mo | Not reported |
| 2y survival | 47% | 41% | ns |
| 5y survival | 26% | 16% | 0.04 |
| Grade 3 oesophagitis | 27% | 11% | Not reported |

Median age 62y, 59% ♂, 90% white; there were 11 treatment-related deaths.

Discussion

The survival rate obtained in this trial exceeded that in any previous large randomized trial of chemotherapy and radiotherapy in small cell lung cancer. A total of 353 deaths had been anticipated at 2y, but, after 5y, only 335 deaths had been reported. Previous studies of concurrent treatment had used cyclophosphamide- or doxorubicin-based chemotherapy with increased toxicity. The newer cisplatin/etoposide regimen used here was better tolerated in combination with radiotherapy, allowing the delivery of full systemic doses of chemotherapy. In addition, commencing radiotherapy early with the first cycle of chemotherapy was thought to be advantageous. (See Table 17.16.)

Problems

- Patients in the twice-daily group received a biologically higher dose of radiotherapy. Would the difference in survival be lost if the once-daily group were treated with an equivalent dose?
- In practice, it is difficult to deliver radiotherapy along with the first chemotherapy cycle, due to treatment planning delay. The second cycle may be a more realistic aim.
- Rates of grade 3 oesophagitis could be decreased by delivering modern three-dimensional (3D) conformal radiotherapy.

Non-small cell lung cancer: chemotherapy

The Big Lung Trial: Chemotherapy versus supportive care in advanced non-small cell lung cancer: improved survival without detriment to quality of life.

AUTHORS: Spiro S, Rudd R, Souhami R et al.

REFERENCE: *Thorax* (2004) **59**, 828–36.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Cisplatin-based chemotherapy improves survival, without detriment to QoL, and is cost-effective in advanced non-small cell lung cancer (NSCLC).

Impact

Platinum-based chemotherapy is recommended for patients with advanced NSCLC and now forms part of standard therapy, alongside a third-generation drug, e.g. gemcitabine.

Aims

A meta-analysis of over 50 RCTs (over 9,000 patients) by the NSCLC Collaborative Group (*BMJ* (1995) **311**, 899–909) had shown survival benefits from cisplatin-based cytotoxic chemotherapy when used alongside surgery (\pm radiotherapy, RT), radical RT, and supportive care; the clearest evidence of positive effect was for regimens containing cisplatin in non-surgical (i.e. relatively advanced) disease. However, the individual studies used differing patient selection criteria and treatment regimens, with limited analysis of QoL and costs. With uncertainty surrounding whether the limited survival benefits had positive impacts on QoL, this study was designed to evaluate the survival benefits of chemotherapy, as well as assessing QoL and costs of treatment.

Methods

Patients: 725 patients from 57 UK and five non-UK centres.

Inclusion criteria: Patients of all stages and performance status for whom supportive care was considered the treatment of choice included:

- Histological or cytological diagnosis of NSCLC;
- Medically unsuitable for (or declined) radical RT or surgery;
- Fit to receive chemotherapy;
- No concurrent or recent significant malignancy.

Groups: Groups matched for gender, age, clinical stage, histology, centre, chemotherapy, and performance status:

- No chemotherapy (NoC) ($n = 361$);
- Three cycles of 3-weekly chemotherapy (C): with cisplatin, mitomycin, and ifosfamide; or cisplatin, mitomycin, vinblastine; or cisplatin, vinorelbine; or cisplatin, vindesine ($n = 364$).

Primary endpoint: Overall survival.

Sub-studies:

- QoL, as judged by validated questionnaires at baseline, 6–8wk, and 12, 18, and 24wk ($n = 273, 135$ C). Primary endpoint: global QoL at 12wk;
- Costs, collected retrospectively from randomization to death or 2y F/U. Included inpatient stays, investigations, chemotherapy, RT, procedures, and hospice care ($n = 194, 99$ C).

Results**Table 17.17** Summary of results

| Primary endpoint | No chemotherapy | Chemotherapy | <i>p</i> |
|---------------------------|-----------------|--------------|--------------|
| 1y survival | 20% | 29% | Not reported |
| 2y survival | 5% | 10% | Not reported |
| Sub-studies | | | |
| QoL score (0–100) at 12wk | 48.2 | 52.1 | 0.4 |
| Cost/wk of life | £149 | £157 | ns |

Baseline: median age = 65y, 74% ♂; stage III or IV = 95% disease: squamous histology = 53%; WHO performance status 0 or 1 = 78%.

Discussion

This study demonstrated chemotherapy to improve median survival from 5.7mo to 8mo. The probability of survival increased almost 50% at 1y and doubled at 2y. Importantly, it showed that this increase in survival was not associated with worse QoL and was cost-effective. The trial confirmed the results of previous meta-analyses in a setting applicable to clinical practice and is consistent with subsequent prospective studies of chemotherapy in NSCLC. (See Table 17.17.)

Problems

- The study included various chemotherapy regimens which were combined in the analysis. Supportive care was determined locally. More recent studies have shown that newer third-generation agents, combined with platinum-based drugs (e.g. gemcitabine and carboplatin), offer superior survival to those included in this trial.
- The authors point out that, despite the lack of change to overall QoL in the chemotherapy group, treatment was associated with a 5% risk of death from drug-related toxicity.
- Despite the clear survival benefit demonstrated, the absolute improvement in median survival following chemotherapy was only 9wk (equal to three cycles of chemotherapy). More recent chemotherapy regimens may offer improved survival or QoL.

Non-small cell lung cancer: epidermal growth factor receptor inhibitors

BR.21 study: Erlotinib in previously treated non-small-cell lung cancer.

AUTHORS: Shepherd F, Pereira J, Ciuleanu T *et al.* (National Cancer Institute of Canada Clinical Trials Group).

REFERENCE: *N Engl J Med* (2005) 353, 123–32.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Erlotinib, an epidermal growth factor receptor (EGFR) inhibitor, prolongs survival (compared with placebo) in patients with NSCLC after first- or second-line chemotherapy.

Impact

Lung cancer is the leading cause of cancer death in the Western world, and survival from NSCLC remains poor. This study demonstrated that non-cytotoxic chemotherapy is useful in the management of NSCLC. EGFR inhibitors offer a novel modality of treatment which may be particularly effective in certain patient groups, sparking great interest in the molecular pathogenesis of lung cancer.

Aims

The USA's FDA had approved the use of EGFR inhibitors for the treatment of NSCLC. This trial was designed to investigate any survival advantage for erlotinib over placebo in patients who had received prior chemotherapy.

Methods

Patients: 731 patients at 72 centres worldwide (National Cancer Institute of Canada Clinical Trials Group).

Inclusion criteria:

- Pathological evidence of NSCLC;
- Previously received one or two regimens of chemotherapy;
- ECOG performance status 0–3.

Exclusion criteria:

- Cerebral metastases;
- Other malignant disease within 5y;
- Cardiac, ophthalmic or GI disease.

Groups: Patients stratified according to centre, performance status, response to prior chemotherapy, number of prior regimens, and previous platinum-based chemotherapy:

- Erlotinib (150mg od) ($n = 488$);
- Placebo ($n = 243$);
- Twenty-two patients were subsequently ineligible.

Primary endpoint: Overall survival.

Secondary endpoints:

- Progression-free survival;
- Response rate (complete and partial) and duration of response;
- Toxic effects;
- QoL.

Follow-up: History, examination, and blood tests were performed every 4wk, and radiological investigations every 8wk for 6mo.

Results

Table 17.18 Summary of results

| Primary endpoint | Placebo | Erlotinib | <i>p</i> |
|----------------------------|---------|-----------|----------|
| Median overall survival | 4.7mo | 6.7mo | <0.001 |
| Secondary endpoints | | | |
| Progression-free survival | 1.8mo | 2.2mo | <0.001 |
| Response rate | <1% | 8.9% | <0.001 |

Baseline: median age = 61y; 65% = ♂; 50% tumours were adenocarcinomas, 30% SCCs; 49% had received two prior chemotherapy regimes; 93% had received cisplatin-based therapy.

Discussion

Erlotinib improved survival in patients with NSCLC who had already received first- or second-line chemotherapy. Overall, 9% of patients responded to erlotinib, but the likelihood of response was much higher among women ($p = 0.006$), lifelong non-smokers ($p < 0.001$), East Asians ($p < 0.02$), and patients with adenocarcinoma ($p < 0.001$). Erlotinib also improved QoL in patients with NSCLC. (See Table 17.18.)

Problems

- 19% on erlotinib (vs 2% on placebo) required dose reductions, due to adverse effects; 12% experienced a rash, and 5% diarrhoea; 5% of patients discontinued erlotinib, because of toxic effects.
- The study did not address the role of the EGFR inhibitor in the most vulnerable patients (performance status 4).
- No head-to-head trials of docetaxel vs erlotinib, although the INTEREST trial (*Lancet* (2008) **372**, 1809–18) showed non-inferior survival on gefitinib (a related EGFR inhibitor), compared with docetaxel, as second-line treatment in patients with NSCLC. The UK's NICE now recommends erlotinib as an alternative to docetaxel after failure of first-line chemotherapy, if the manufacturer provides erlotinib at the same cost.

Rheumatology

Introduction 486

Rheumatoid arthritis: tumour necrosis factor- α antagonists 488

Rheumatoid arthritis: comparison of tumour necrosis factor- α antagonists 490

Rheumatoid arthritis: infliximab 492

Rheumatoid arthritis: early treatment 494

Rheumatoid arthritis: B-cell-targeted therapy 496

Arthritis: cardiovascular outcomes with drug therapies 498

Ankylosing spondylitis: tumour necrosis factor- α antagonists 500

Gout: NSAIDs and COX-2 inhibitors 502

Scleroderma lung disease: cyclophosphamide 504

Painful shoulder: corticosteroid injection vs physiotherapy 506

Introduction

In the fourth century BC, the Greek physician Hippocrates developed a medical theory called humoralism, which held that four humors (liquids) coursing through the human body determined a person's temperament and state of health. He used the term *rheuma*, which literally means 'flowing', to describe an excess of the watery humor thought to flow down from the brain. The words *rheuma* and *catarrhos* ('flowing down') were used interchangeably by ancient Greeks to describe a variety of illnesses, including joint problems. The French physician Ballonius in 1642 coined the term 'rheumatism' and distinguished noxious humors that affected joints from those that caused *catarrh* (hay fever, head colds, and sinusitis).

Thomas Sydenham (1624–89), a London physician who himself suffered from gout, distinguished the acute arthritis that attacked young people (probably rheumatic fever) from a chronic, crippling arthritis (probably rheumatoid arthritis, RA) that came to be called rheumatic gout. Another British physician AB Garrod, whose practice was devoted to studying 'articular affections', introduced the term 'rheumatoid arthritis' (from the Greek *arthron*, 'joint') in 1858 because, he insisted, the majority of patients said to have 'rheumatic gout' had an affliction that was related 'neither to true gout nor to true rheumatism.' Osteoarthritis (from the Greek *osteon*, 'bone') was commonly used as a synonym for RA. A clear distinction between the two ailments emerged at the beginning of the twentieth century. In 1904, a Boston physician Joel E Goldthwait described the differences he saw using X-rays. In 1909, the physicians Edward H Nichols and Frank L Richardson of New York reported on the pathological differences between osteoarthritis and RA. Today, there are clear criteria established for the clinical manifestations of rheumatic diseases, but there is still a long way to go in terms of establishing a clear understanding of their pathogenesis.

Rheumatoid arthritis: tumour necrosis factor- α antagonists

PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment.

AUTHORS: Breedveld F, Weisman M, Kavanaugh A et al.

REFERENCE: *Arthritis Rheum* (2006) 54, 26–37.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

In patients with early (<3y), aggressive RA, combination therapy with adalimumab and methotrexate (MTX) is significantly superior to either MTX alone or adalimumab alone in improving signs and symptoms, inhibiting radiographic progression, and effecting clinical remission.

Impact

TNF- α antagonists are now routinely used in the treatment of RA in patients who have active disease. The best efficacy is achieved when they are used in combination with MTX.

Aims

Both the TNF- α antagonist adalimumab and MTX had previously been shown to be effective in the treatment of RA. However, no trial had assessed their use in combination. This trial explored the effectiveness of combination therapy in the treatment of early, aggressive RA.

Methods

Patients: 799 patients recruited from 133 international centres.

Inclusion criteria:

- Diagnosis of RA (according to the 1987 American College of Rheumatology (ACR) criteria);
- Disease duration <3y;
- Age ≥ 18 y;
- Active disease with ≥ 8 swollen joints and ≥ 10 tender joints, plus one of: early morning stiffness for >45min; erythrocyte sedimentation rate (ESR) >28mm/h; CRP >15mg/L;
- Rheumatoid factor +ve or erosion of at least one joint.

Exclusion criteria:

- Previous immunosuppressant/disease-modifying anti-rheumatic drug (DMARD) therapy;
- Active infections, including TB.

Groups: All patients received concomitant folic acid 5–10mg/wk:

- Adalimumab 40mg SC fortnightly + MTX 20mg/wk ($n = 268$);
- Adalimumab 40mg SC fortnightly + placebo ($n = 274$);
- Placebo SC fortnightly + MTX 20mg/wk ($n = 257$).

Primary endpoints: 50% improvement (ACR50) at 1y and mean change in baseline of the modified Sharp score (a measure of joint damage assessed radiographically, based on joint space narrowing and erosions).

Secondary endpoints: Percentage of patients achieving clinical remission (28-joint Disease Activity Score (DAS-28) < 2.6), improvement in physical function measured by the health assessment questionnaire, and ACR20, ACR50, ACR70, and ACR90 responses at 2y.

Follow-up: 2y.

Results

- At 1y, 62% of patients receiving combination therapy exhibited an ACR50 response vs 46% receiving MTX alone or 41% receiving adalimumab alone ($p = 0.001$). Similar effects on ACR20, ACR70, and ACR 90 response rates were observed at 2y;
- There was also significantly less radiographic progression among patients on combination treatment after 1 and 2y (1.3 and 1.9 Sharp units, respectively), when compared with patients on MTX alone (5.7 and 10.4 Sharp units) or adalimumab alone (3 and 5.5 Sharp units) ($p \leq 0.002$);
- 49% of patients on combination therapy displayed disease remission (DAS-28 < 2.6) at 2y, while only 25% displayed remission in the MTX alone or adalimumab alone groups.

Discussion

This study provided evidence that early use of a TNF- α antagonist could induce remission in almost half the patients treated with adalimumab in combination with concomitant MTX.

Problems

- Further long-term data are required to establish the durability of remission on this drug combination, as well as long-term cost-effectiveness.
- Despite impressive data from this study illustrating better outcomes in poor-prognosis patients with RA treated early with combination therapy, the current UK's NICE guidelines state that patients have to 'fail' with two DMARDs prior to anti-TNF- α therapy, thereby delaying the widespread introduction of TNF inhibitors.

Rheumatoid arthritis: comparison of tumour necrosis factor- α antagonists

TEMPO (Trial of Etanercept and Methotrexate with radiographic Patient Outcomes) study: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis.

AUTHORS: Klareskog L, van der Heijde D, Jager J *et al.*

REFERENCE: *Lancet* (2004) **363**, 675–81.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Treatment with a combination of etanercept and methotrexate (MTX) is superior in the treatment of RA than either agent alone.

Impact

TNF- α antagonists are now routinely used in the treatment of RA in patients who have active disease.

Aims

Etanercept is a human soluble dimeric TNF type II receptor fusion protein, linked to the IgG1-Fc fragment. It binds to, and inactivates, TNF. Both etanercept and MTX have previously been shown to be effective in the treatment of RA. This trial aimed to explore their effectiveness when used in combination.

Methods

Patients: 686 patients from numerous international centres.

Inclusion criteria:

- Diagnosis of RA (according to the 1987 ACR criteria);
- Age ≥ 18 y, with disease duration 6mo to 20y;
- Active disease with ≥ 10 swollen joints and ≥ 12 tender joints plus one of: early morning stiffness for >45 min; ESR >28 mm/h; C-reactive protein (CRP) >20 mg/L;
- Failure of at least one DMARD other than MTX;
- Not treated with MTX in the previous 6mo.

Exclusion criteria:

- Immunosuppressant therapy in the preceding 6mo;
- Previous treatment with any anti-TNF- α agent;
- Treatment with an investigational or biologic agent in the preceding 3mo;
- Treatment with DMARD or corticosteroid in the preceding 4wk;
- Active infections.

Groups: All patients received 5mg folic acid twice a week:

- MTX 7.5mg weekly, escalated to 20mg weekly within 8wk, if the patient had painful or swollen joints + SC placebo twice a week ($n = 228$);
- Etanercept 25mg SC twice a week plus oral placebo tablet weekly ($n = 223$);
- MTX + etanercept ($n = 231$).

Primary endpoint: Numeric index of the ACR response (ACR-N) area under the curve (AUC) over the first 24wk. Radiographic endpoint was the change in total joint damage score (modified total Sharp score = joint erosion + joint space narrowing score) over 52wk.

Follow-up: Every 4wk for 30wk.

Results

- ACR-N AUC at 24wk was greater for the combination group vs etanercept or MTX alone (18.3%-y [95% CI 17.1–19.6] vs 14.7%-y [13.5–16], $p < 0.0001$, and 12.2%-y [11.0–13.4], $p < 0.0001$, respectively);
- The combination was more efficacious than MTX or etanercept alone in retardation of joint damage (mean total Sharp score -0.54 [95% CI -1.00 to -0.07] vs 2.8 [1.08–4.51], $p < 0.0001$, and 0.52 [-0.1 to 1.15], $p = 0.0006$, respectively);
- The number of patients reporting infections or adverse events was similar in all groups.

Discussion

This study added another therapeutic option in the treatment of active RA. It showed that combination therapy with etanercept and MTX was superior to either agent alone. This observation emphasized the importance of co-prescribing MTX, when tolerated, even at modest doses, in order to achieve synergy with an anti-TNF- α agent such as etanercept.

Problems

- Use of anti-TNF- α agents is expensive (in the UK, costs are £8,000/y, compared with MTX at £20/y). Use of anti-TNF therapies has significant economic implications which may result in some degree of rationing.
- The study population comprised an unusually high proportion of patients in the established phase of disease without prior exposure to MTX. Such a population does not reflect the typical DMARD-refractory patient considered for anti-TNF therapy in routine clinical practice.

Rheumatoid arthritis: infliximab

ATTRACT (Anti-TNF Trial in Rheumatoid Arthritis with Concomitant Therapy): Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate.

AUTHORS: Maini R, St Clair W, Breedveld F et al. (ATTRACT study group).

REFERENCE: *Lancet* (1999) 354, 1932–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Treatment with infliximab and methotrexate (MTX) is more effective than MTX alone in patients with uncontrolled active RA.

Impact

TNF- α antagonists are now routinely used in the treatment of RA in patients who have active disease, despite the use of conventional disease-modifying drugs.

Aims

Many patients with RA fail to respond to, or are unable to tolerate, conventional disease-modifying therapy such as MTX. This study aimed to investigate whether a chimeric human–mouse monoclonal antibody to TNF- α (infliximab) provided clinical benefit in patients with active disease.

Methods

Patients: 428 patients from 34 international centres.

Inclusion criteria: Active RA:

- Diagnosis of RA (according to the 1987 ACR criteria);
- Active disease with ≥ 6 swollen joints, plus two of: early morning stiffness for >45 min, ESR >28 mm/h, CRP >2 mg/dL;
- Stable dose of MTX (at least 12.5 mg/wk PO/IM);
- Stable dose of folic acid for at least 4 wk;
- Receiving both drugs for at least 3 mo;
- If oral corticosteroids (dose of 10 mg/kg or less) or NSAIDs were used, then the dose must have been stable for 4 wk prior to screening;
- Hb >5.3 mmol/L, WBC $>3.5 \times 10^9$ /L, neutrophils $>1.5 \times 10^9$ /L, aspartate transaminase (AST) and ALP $<2 \times$ the upper limit of normal, creatinine <150 micromol/L.

Groups: All patients received IV infusions at wk 0, 2, and 6:

- Infliximab 3 mg/kg every 4 wk ($n = 86$) or 8 wk ($n = 85$);
- Infliximab 10 mg/kg every 4 wk ($n = 81$) or 8 wk ($n = 87$);
- Placebo ($n = 88$).

Primary endpoint: 20% improvement, as defined by the ACR (ACR20) at wk 30.

Secondary endpoints:

- 50% and 70% improvement, as defined by the ACR (ACR50 and ACR70);
- Reduction in individual measurements of disease severity;
- General health assessment.

Follow-up: Every 4wk for 30wk.

Results**Table 18.1** Summary of results

| Primary endpoint | Placebo | Infliximab 3mg/kg every 8wk | Infliximab 3mg/kg every 4wk | Infliximab 10mg/kg every 8wk | Infliximab 10mg/kg every 4wk |
|----------------------------|---------|-----------------------------|-----------------------------|------------------------------|------------------------------|
| ACR20 | 20% | 50% | 53% | 52% | 58% |
| <i>p</i> | — | <0.001 | <0.001 | <0.001 | <0.001 |
| Secondary endpoints | | | | | |
| ACR50 | 5% | 27% | 29% | 31% | 26% |
| <i>p</i> | — | <0.001 | <0.001 | <0.001 | <0.001 |
| ACR70 | 0% | 8% | 11% | 18% | 11% |
| <i>p</i> | — | 0.007 | 0.002 | <0.001 | 0.002 |

Discussion

While conventional treatments, such as MTX, are effective, some patients develop adverse reactions, and others maintain disease activity with resultant erosive destruction and deformation of joints. Uncontrolled RA also leads to an increase in mortality. TNF- α antagonists have revolutionized treatment of these patients, improving symptoms and inhibiting joint destruction. More recent studies (*Arthritis Rheum* (2003) **48**, 35–45) have demonstrated the efficacy of the fully human anti-TNF- α monoclonal antibody adalimumab. This has the advantage of being administered by SC injection. (See Table 18.1.)

Problems

- Although there was no difference in the number of serious adverse events between placebo and infliximab groups in this trial, subsequent experience indicates that infliximab may predispose to unusual infections, including reactivation of TB.
- In this study, low levels of double-stranded DNA were induced in a small proportion of patients. Drug-induced lupus is rare, resolving with cessation of infliximab and treatment with steroids, as required.
- Infliximab is contraindicated in patients with MS, as it may precipitate demyelinating episodes.
- The efficacy of infliximab may decrease with repeated infusions over time, because of the formation of human antichimeric antibodies.

Rheumatoid arthritis: early treatment

BeSt ('Behandel Strategieën'—Dutch acronym for 'best strategy') study:

Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis.

AUTHORS: Goekoop-Ruiterman Y, de Vries-Bouwstra J, Allart C et al.

REFERENCE: *Arthritis Rheum* (2005) 52, 3381–90.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Patients with early RA show faster improvement of function and inhibition of radiographic joint damage when treated with combination disease-modifying therapy, including either prednisolone or infliximab.

Impact

Optimized suppression of synovitis at the onset of RA leads to superior outcomes.

Aims

The approach to RA management has changed from just symptom relief to prevention of long-term complications. This study aimed to establish whether combination drugs provided more clinical and radiographic benefit than single agents in the treatment of early RA. Additionally, it aimed to establish whether corticosteroids and TNF- α agents should be part of this early aggressive treatment.

Methods

Patients: 508 patients from 18 peripheral and two university hospitals in the western Netherlands.

Inclusion criteria: Active RA:

- Diagnosis of RA (according to the 1987 ACR criteria);
- Age >18 y;
- Disease duration ≤ 2 y;
- Active disease: $\geq 6/68$ tender joints and either ESR ≥ 28 mm/h or global health score ≥ 20 mm.

Groups:

- Group 1 (sequential monotherapy): One drug at a time, starting with MTX, switching to other drugs if no improvement (sulfasalazine, leflunomide, then MTX with infliximab, if necessary) ($n = 126$);
- Group 2 (step-up combination regimen): Beginning on MTX, with more drugs added as necessary (sulfasalazine, then hydroxychloroquine, then prednisolone, then switching to MTX with infliximab) ($n = 121$);
- Group 3 (combination therapy with prednisolone): Started immediately on a combination of MTX, sulfasalazine, and tapered high-dose

prednisolone (switching sulfasalazine for ciclosporin, if necessary, and then to MTX with infliximab) ($n = 133$);

- Group 4 (combination therapy with infliximab): Combination therapy from the beginning with MTX and infliximab (and then, if necessary, leflunomide, sulfasalazine, ciclosporin, and prednisolone) ($n = 128$).

Primary endpoint: Functional ability, measured by the Dutch version of the Health Assessment Questionnaire (D-HAQ), and radiographic damage according to the modified Sharp/Van der Heijde score. The latter was assessed on radiographs of the hands and feet obtained at baseline and 1y.

Follow-up: Every 3mo and treatment adjusted according to DAS-44. Therapy intensified if DAS-44 ≤ 2.4 .

Results

Table 18.2 Summary of results

| | Mean D-HAQ score | | <i>p</i> |
|-----|------------------|--------------|---|
| | Groups 1 + 2 | Groups 3 + 4 | |
| 3mo | 1.0 | 0.6 | 1 + 2 vs 3 + 4; $p < 0.001$ |
| 1y | 0.5 | 0.5 | 1 vs 3; $p = 0.01$ 1 vs 4; $p = 0.003$ |

- In the first year of F/U, patients treated with initial combination therapy, including prednisolone (group 3) or infliximab (group 4), had less progression of radiographic joint damage. (See Table 18.2.)

Discussion

Patients treated by initial combination therapy with either prednisolone or infliximab had more functional improvement than patients treated with sequential monotherapy or step-up combination therapy. Patients were less likely to progress to joint erosions after initial combination therapy with either prednisolone or infliximab. There were no benefits of step-up combination therapy over sequential monotherapy in terms of symptom improvement or inhibition of radiographic damage.

Problems

Despite the favourable outcomes achieved with step-down combination therapy using a tapered prednisolone regime, many patients dislike the SEs associated with steroids.

Rheumatoid arthritis: B-cell-targeted therapy

Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis.

AUTHORS: Edwards J, Szczepanski L, Szechinski J *et al.*

REFERENCE: *N Engl J Med* (2004) **350**, 2572–81.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Treatment with the anti-CD20 monoclonal antibody rituximab is effective in patients with uncontrolled active RA, despite treatment with methotrexate (MTX).

Impact

Rituximab is now approved in the treatment of severe uncontrolled active RA when TNF- α antagonists have failed.

Aims

Rituximab is an anti-CD20 monoclonal antibody used in the treatment of CD20⁺ B-cell NHL. CD20 is a B-cell surface antigen that is expressed only on pre-B and mature B cells. The aim of this trial was to confirm previous (non-RCT) observations that selective depletion of B-cells with the use of rituximab leads to sustained clinical improvements for patients with RA.

Methods

Patients: 161 patients from 26 rheumatology centres in 11 countries.

Inclusion criteria: Active RA despite treatment with MTX:

- Diagnosis of RA (according to the 1987 ACR criteria).
- Age >21y;
- Seropositive rheumatoid factor ≥ 20 IU/mL;
- Active disease defined by ≥ 8 swollen joints, eight tender joints on ≥ 10 mg MTX, and ≥ 2 of the following:
 - CRP level ≥ 15 mg/L;
 - ESR ≥ 28 mm/h;
 - Early morning stiffness >45 min.

Exclusion criteria:

- Diagnosis of autoimmune disease, other than RA;
- American Rheumatism Association functional class IV disease;
- Rheumatoid vasculitis, active infection, immunodeficiency, history of malignancy.

Groups: All patients received a 17d course of steroids and one dose of folinic acid:

- MTX alone ≥ 10 mg/wk ($n = 40$);
- Rituximab alone 1g on d 1 and 15 ($n = 40$);

- Rituximab on d 1 and 15 + cyclophosphamide 750mg on d 3 and 17 ($n = 41$);
- Rituximab on d 1 and 15 + MTX $\geq 10\text{mg/wk}$ ($n = 40$).

Primary endpoint: Proportion of patients with an ACR50 response (50% improvement) at wk24.

Secondary endpoints:

- 20% and 70% improvement defined by ACR20 and ACR70;
- Change in DAS-28.

Follow-up: Clinical assessments at baseline, and wk12, 16, 20, and 24.

Results

Table 18.3 Summary of results

| | % attaining score at wk 24 | | Change in score at wk 24 |
|------------------------------|----------------------------|--------------------|------------------------------|
| | ACR50 | ACR20 | DAS-28 |
| MTX | 13 | 38 | -1.39 to 1.2 |
| Rituximab | 33 ($p = 0.005$) | 65 ($p = 0.03$) | -2.29 to 1.4 ($p = 0.002$) |
| Rituximab + cyclophosphamide | 41 ($p = 0.005$) | 76 ($p = 0.001$) | -2.69 to 1.5 ($p = 0.002$) |
| Rituximab + MTX | 43 ($p = 0.005$) | 73 ($p = 0.003$) | -2.69 to 1.3 ($p = 0.001$) |

p -values compared with MTX alone.

Discussion

This trial demonstrated that two doses of rituximab, alone or in combination with cyclophosphamide or MTX, provided a significant and enduring improvement in the symptoms of RA. Additionally, this effect was sustained for up to 48wk. The study also identified B-cells as a key contributor to the immunopathogenesis of RA. (See Table 18.3.)

Problems

Depletion of B-cells may result in long-term effects on the acquired immune system, and careful monitoring is required. However, this study showed a similar incidence of infection in rituximab-treated and control groups at wk 24 and 48.

Arthritis: cardiovascular outcomes with drug therapies

MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term) programme: Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis.

AUTHORS: Cannon C, Curtis S, FitzGerald G *et al.*

REFERENCE: *Lancet* (2006) **368**, 1771–81.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Rates of thrombotic cardiovascular (CV) events in patients with osteoarthritis or RA on the COX-2 inhibitor etoricoxib are similar to those in patients on long-term diclofenac.

Impact

Etoricoxib can be used with caution in patients at risk of thrombotic vascular events.

Aims

Studies had shown increased rates of thrombotic CV complications with COX-2 inhibitors. However, comparable data for the use of NSAIDs were not present. This study aimed to compare the relative risk of thrombotic CV events with etoricoxib and diclofenac using a non-inferiority trial design.

Methods

Patients: 34,701 patients from 1,380 sites in 46 countries (patients combined from three trials: MEDAL, EDGE, and EDGE II).

Inclusion criteria:

- Diagnosis of RA according to the 1987 ACR criteria;
- Diagnosis of osteoarthritis of the knee, hip, hand, or spine;
- Age ≥ 50 y;
- Low-dose aspirin was recommended for prophylaxis in patients with established CV, peripheral arterial, or cerebrovascular disease.

Groups:

- Etoricoxib ($n = 17,412$);
- Diclofenac ($n = 17,289$).

Primary endpoint: Comparison of thrombotic CV events with etoricoxib and diclofenac.

Follow-up: Every 4mo for 3.5y.

Results

- The HR of thrombotic events in the two groups was 0.95 (95% CI 0.81–1.11), showing non-inferiority of etoricoxib to diclofenac.

Discussion

This large study showed no difference in the CV thrombotic rates of diclofenac and etoricoxib treatment in patients with osteoarthritis and RA.

Problems

- This study did not have a placebo group; hence, it was not possible to estimate absolute CV risks associated with etoricoxib and diclofenac.
- Increased CV risk has been demonstrated with other similar agents, including rofecoxib and valdecoxib. However, in light of the findings in the MEDAL programme, it cannot be assumed that this is a class effect.
- In the VIGOR study, the COX-2 inhibitor rofecoxib was compared with naproxen when more CV events were observed in the rofecoxib group. The explanation for this could be 3-fold. Firstly, rofecoxib promotes intravascular thrombosis. Secondly, naproxen is protective against these thromboses, or thirdly both the previous considerations might apply. It would be interesting to compare etoricoxib with naproxen in terms of CV outcomes.

Ankylosing spondylitis: tumour necrosis factor- α antagonists

Treatment of active ankylosing spondylitis with infliximab: a randomised controlled multicentre trial.

AUTHORS: Braun J, Brandt J, Listing J, *et al.*

REFERENCE: *Lancet* (2002) 359, 1187–93.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Infliximab improves the disease activity index in patients with active ankylosing spondylitis despite treatment with NSAIDs.

Impact

The first trial to show the effectiveness of TNF- α antagonists in the treatment of ankylosing spondylitis, providing a therapeutic option for patients with uncontrolled pain and inflammation.

Aims

There are few treatment options for ankylosing spondylitis. Infliximab, a monoclonal antibody to TNF- α , had already been used with great success in other chronic inflammatory conditions such as RA. This trial aimed to assess the role of infliximab in the treatment of ankylosing spondylitis.

Methods

Patients: 70 patients recruited from multiple centres in Germany.

Inclusion criteria:

- Diagnosis of ankylosing spondylitis, as defined by New York criteria (1984);
- Bath ankylosing spondylitis disease activity index (BASDAI) ≥ 4 ;
- Spinal pain, as assessed on 10cm VAS.

Exclusion criteria:

- Active TB within the previous 3y;
- Specific chest X-ray changes;
- Serious infections in the previous 2mo;
- History of malignant disease in the previous 5y.

Groups: Drugs were administered at 0, 2, and 6wk:

- Infliximab ($n = 34$);
- Placebo ($n = 35$).

Primary endpoint: 50% improvement in BASDAI.

Secondary endpoints: Improvement in VAS for spinal pain, Bath ankylosing spondylitis functional index (BASFI), Bath ankylosing spondylitis metrology index (BASMI), SF36, CRP, and ESR.

Follow-up: At 2, 6, and 12wk.

Results

Table 18.4 Summary of results

| | 50% BASDAI improvement at wk 12 | 95% CI | Baseline BASDAI | Wk 12 BASDAI |
|--------------|------------------------------------|--------|--------------------|-----------------|
| Infliximab | 53% | 37–69% | 6.5 | 3.3 |
| Placebo | 9% | 3–22% | 6.3 | 5.7 |
| $p < 0.0001$ | | | | |

- BASFI and BASMI showed similar differences. (See Table 18.4.)

Discussion

There have been very few randomized studies of disease-modifying drugs in the treatment of ankylosing spondylitis. This study showed infliximab to significantly reduce disease activity, and improve function and QoL in patients who were chronically ill and partly disabled by ankylosing spondylitis.

Problems

- This was a short-term trial. Therefore, long-term effectiveness of infliximab and its effects on radiographic progression of disease could not be assessed. Subsequent studies show sustained improvement in function, although TNF blockade does not arrest progression of radiographic axial damage.

Gout: NSAIDs and COX-2 inhibitors

Safety and effectiveness study: Randomised double blind trial of etoricoxib and indometacin in treatment of acute gouty arthritis.

AUTHORS: Schumacher H, Boice J, Daikh D et al.

REFERENCE: *BMJ* (2002) 324, 1488–92.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The COX-2 inhibitor etoricoxib is comparable to indometacin in the effective and rapid treatment of gouty arthritis.

Impact

Etoricoxib is now used in the treatment of gout where classical NSAIDs are contraindicated.

Aims

The NSAID indometacin had been established as the most commonly used treatment for gout, despite limited studies demonstrating its efficacy. COX-2 inhibitors had been proposed to have efficacy in treating acute inflammatory conditions without some of the GI SEs of NSAIDs. This study aimed to assess the safety and efficacy of a selective COX-2 inhibitor, compared with the gold standard treatment indometacin, in the treatment of acute gouty arthritis.

Methods

Patients: 142 men and eight women from 43 outpatient centres in 11 countries.

Inclusion criteria:

- Age ≥ 18 y;
- Diagnosis of acute gout (onset within 48h) associated with moderate or severe pain;
- Sum score ≥ 5 for pain (0–4 point scale), tenderness (0–3 point scale), and swelling (0–3 point scale);
- No clinically significant abnormalities of blood count, chemistry, and urinalysis.

Exclusion criteria:

- Polyarticular gout involving >4 joints;
- Concurrent medical or arthritic disease;
- Unstable medical condition;
- CVA or MI in the preceding year;
- Patients on antiplatelet or anticoagulant therapy, digoxin, or corticosteroids (1mo previously).

Groups:

- Indometacin (50mg tds) ($n = 75$);
- Etoricoxib (120mg od) ($n = 75$).

Primary endpoint: Patient's assessment of pain in the study joint (0–4 point scale: none/mild/moderate/severe/extreme) 4h after initial dose on d 1, and then 4h after the first dose on d 2 to 8.

Secondary endpoints: Investigator's assessment of the study joint on the basis of palpation or passive movement, swelling, and erythema, and the patient's and investigator's global assessment of response to treatment.

Follow-up: d 2, 5, 8, and 14.

Results

- Patient's assessment of pain in the study joint over d 2 to 5 showed a mean change from baseline of -1.72 (95% CI -1.9 to -1.55) for etoricoxib and -1.83 (-2.01 to -1.65) for indometacin.
- Etoricoxib showed efficacy similar to indometacin for all 2° efficacy endpoints.

Discussion

This was the largest controlled trial in gout reported to date. It found that the efficacy of etoricoxib was comparable to that of indometacin, with significantly fewer drug-related adverse effects in the etoricoxib group. In practice, it may be more convenient for patients to take a once-daily formulation, and etoricoxib is likely to be a popular choice in the treatment of acute gout. The study was well designed, because emphasis was placed on drug effects during the initial days of the acute gouty attack. This is important, because acute gout is usually a self-limiting condition.

Problems

- One limitation of the study was that patients with polyarticular gout were excluded. Therefore, it is difficult to conclude whether the efficacy of the COX-2 inhibitor etoricoxib was equivalent to indometacin in this patient population.
- Many patients with gout are also at risk of CV complications, and such patients were excluded from this study. Given the concern about the association of COX-2 inhibitors with thrombotic events, further safety evaluation studies should be undertaken.

Scleroderma lung disease: cyclophosphamide

Cyclophosphamide versus placebo in scleroderma lung disease.

AUTHORS: Tashkin D, Elashoff R, Clements P *et al.*

REFERENCE: *N Engl J Med* (2006) **354**, 2655–66.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Oral cyclophosphamide has some beneficial effect on lung function, dyspnoea, skin thickening, and health-related QoL in patients with symptomatic scleroderma-related interstitial lung disease.

Impact

Cyclophosphamide is used to improve QoL in the treatment of scleroderma-related lung disease.

Aims

Cyclophosphamide had been the only treatment to date to show promise in the treatment of scleroderma-related interstitial lung disease in a number of retrospective studies. This study aimed to provide definitive evidence regarding the efficacy, toxicity, and risk–benefit ratio of cyclophosphamide in scleroderma lung disease.

Methods

Patients: 158 patients from 13 clinical centres in the USA.

Inclusion criteria:

- Diagnosis of limited or diffuse systemic scleroderma with evidence of active alveolitis on examination of bronchoalveolar lavage fluid or high-resolution CT;
- FVC between 45% and 85% of predicted;
- Grade 2 exertional dyspnoea (according to the baseline instrument of the Mahler Dyspnoea Index).

Exclusion criteria:

- Single-breath carbon monoxide diffusion capacity <30% predicted;
- History of smoking in preceding 6mo;
- Clinically significant pulmonary HTN requiring treatment;
- Patients taking prednisolone >10mg/d, previous cyclophosphamide treatment, and previous potentially disease-modifying treatment.

Groups:

- Oral cyclophosphamide (1mg/kg/d, increased monthly up to 2mg/kg/d) (*n* = 79);
- Placebo (*n* = 79).

Primary endpoint: FVC expressed as a percentage of predicted at 12mo.

Secondary endpoints:

- Health Assessment Questionnaire (HAQ) disability index;
- Skin thickening.

Follow-up: 3-monthly for 12mo.

Results

- A total of 145 patients completed at least 6mo of treatment;
- The mean absolute difference in adjusted 12mo FVC % predicted between the cyclophosphamide and placebo groups was 2.53% (95% CI 0.28–4.79%), favouring cyclophosphamide ($p < 0.03$);
- There was no effect on measures of gas transfer, but there was a significant improvement in dyspnoea, skin thickening, and HAQ disability index in the cyclophosphamide-treated group.

Discussion

While the effect of cyclophosphamide was modest in scleroderma-related interstitial lung disease, there was a marked improvement in QoL. Therefore, this double-blinded study concluded that this agent should be considered in the treatment of inflammatory lung disease 2° to scleroderma.

Problems

It would have been interesting to follow up these patients over a longer period, in order to determine whether benefit was also seen in mortality, and also to assess the long-term SE profile of cyclophosphamide.

Painful shoulder: corticosteroid injection vs physiotherapy

Effectiveness of corticosteroid injections versus physiotherapy for treatment of painful stiff shoulder in primary care

AUTHORS: van der Windt D, Koes B, Devillé W *et al.*

REFERENCE: *BMJ* (1998) 317, 1292–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Intra-articular corticosteroid injections are superior to physiotherapy in the treatment of painful stiff shoulder syndromes.

Impact

Corticosteroid injections could be used as an early treatment in the management of painful shoulder syndrome.

Aims

Painful stiff shoulder (or capsular) syndrome is characterized by painful restriction of passive motion, particularly lateral rotation and abduction. With limited comparative data, this trial aimed to compare two common interventions in the treatment of this syndrome: intra-articular steroid injection and physiotherapy.

Methods

Patients: 109 patients consulting GPs from 40 practices in The Netherlands.

Inclusion criteria:

- Age ≥ 18 y;
- Painful passive glenohumeral mobility, with limited lateral rotation more restricted than abduction and medial rotation.

Exclusion criteria:

- Bilateral symptoms;
- Positive painful arc or resistance tests or loss of power;
- Corticosteroid or physiotherapy in the preceding 6mo;
- Contraindications to treatment;
- T1DM.

Groups:

- Physiotherapy ($n = 56$);
- Corticosteroid injection (40mg of triamcinolone acetate via the posterior approach) ($n = 53$).

Primary endpoint: Outcome at 3 and 7wk, as assessed by patient on a 6-point Likert scale and 100mm VAS (100 = very severe pain). Functional disability was evaluated with a shoulder disability questionnaire (a 16-item scale consisting of common situations that might cause shoulder pain).

Secondary endpoints: An independent observer scored the overall clinical severity of the disorder on a VAS after a physical examination of the patient.

Follow-up: At baseline, then 3, 7, 13, 26, and 52wk.

Results

- At 7wk, 77% treated with injections were deemed to be improved, compared with 46% treated with physiotherapy.
- However, by 52wk, the differences between the two interventions were relatively small.

Discussion

Intra-articular steroid injections may be preferable to physiotherapy in the initial treatment of painful stiff shoulder, because they provide comparatively quick relief of symptoms. However, long-term effects of the two treatments were demonstrated to be similar.

Problems

Little is known about the long-term effectiveness and adverse event profile of the two interventions. Specifically, more data are required regarding the likelihood of recurrence and the effects of repeated steroid injections on tendon integrity.

Part 3

Paediatrics

Paediatrics

- Introduction 512
- Apnoea of prematurity and cerebral palsy: caffeine therapy 514
- Perinatal asphyxial encephalopathy: hypothermia 516
- Cystic fibrosis: early diagnosis, growth and nutrition 518
- Sudden infant death syndrome: sleeping position 520
- Immunization: rotavirus vaccination 522
- Maternal–infant transmission of HIV: zidovudine 524
- Congenital cytomegalovirus: intravenous ganciclovir 526
- Kawasaki disease: addition of prednisolone 528
- Virus-induced wheeze: prednisolone 530
- Resuscitation of the sick child: fluids boluses in Africa 532

Introduction

The oft-heard refrain that ‘children aren’t just little adults’ holds just as true with EBM. When we first started researching this chapter, we thought we would have a profusion of trials from which to choose. However, even after asking numerous specialty and general paediatric colleagues, we found very few large ‘blow you over’ practice-changing RCTs.

Including children in RCTs has obvious complications. Balancing competing requirements is especially challenging, when designing research questions in paediatric trials. For example, it is harder to argue for the greater good when a 3-year-old is having an extra blood test to monitor outcomes when they cannot consent to the test. Indeed, in large trials, children are often excluded, because of the difficulties in obtaining consent. Closer examination reveals that the consent issue is just one of many that might hinder the involvement of children in RCTs. In the long run, this is detrimental to children’s health, as too much clinical practice is extrapolated from adult medicine, with GPs and paediatricians taking the all too common route of prescribing off licence.

This chapter identifies and examines these issues with the aims of:

- Encouraging researchers to appropriately involve children in their research;
- Helping researchers improve the quality of trials involving children.

Such issues include:

- Diversity—spanning premature babies weighing only 500g through to adolescents;
- Dynamic child development—patients go through dramatic developmental changes over months and years, with implications for the length of follow-up;
- Ethical concerns—the participant is rarely able to give informed consent for themselves, and parents act as proxies;
- Emotional factors—at the time of trial recruitment, parents are often under considerable stress;
- Societal context—children occupy a unique position within the family and wider society;
- Vulnerability—sadly children are at risk of abuse—a condition with significant morbidity and mortality that cannot be studied with the ‘gold standard’ of RCT;
- Wide range of pathologies—from the rare congenital abnormalities and genetic syndromes to common infections;
- Global context—contrasting aetiologies, severity of disease, and health resources mean what works in one setting cannot be assumed to do the same elsewhere;

- Practical issues—venepuncture of significant volumes of blood for research assays cannot be taken for granted in either neonates or feisty toddlers. Long-term radiation risks mean radiological investigations need to be carefully considered.

Although such issues can complicate research, they also highlight the individual care and attention that children receive and the need for a holistic perspective. We are grateful the editors saw fit to include this fresh paediatrics chapter in this second edition.

Apnoea of prematurity and cerebral palsy: caffeine therapy

Long-term effects of caffeine therapy for apnoea of prematurity.

AUTHORS: Schmidt B, Roberts B, Davis P *et al.*

REFERENCE: *N Engl J Med* (2007) **357**, 1893–902.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In infants with very low birthweight, caffeine therapy improves the rate of survival, without neurodevelopmental disability, when assessed at 18–21mo of age.

Impact

In addition to the respiratory benefits of caffeine in apnoea of prematurity and decreasing bronchopulmonary dysplasia, this was the first study of a drug that prevents disability in premature babies.

Aims

Prematurity occurs in ~5 of every 1,000 live-born babies, with many weighing only 500–1,250g. Thirty to 40% of these high-risk infants die or survive with life-debilitating conditions—the target population of this study. Although methylxanthines, such as caffeine, have long been used to reduce or treat apnoea in premature infants, little has been established regarding their long-term safety and efficacy. Methylxanthines block adenosine (required for cerebral protection during hypoxic episodes), therefore the consequences on neurodevelopment were unknown. This study aimed to provide long-term F/U data for *N Engl J Med* (2006) **354**, 2112–21, which assessed the impact of caffeine on survival, without neurodevelopmental disability, at a corrected age of 18–21mo.

Methods

Patients: 2,000 patients at multiple international centres.

Inclusion criteria:

- Birthweight 500–1,250g;
- Post-natal age d 1 to 10;
- Considered a candidate for methylxanthine therapy by clinical staff.

Exclusion criteria:

- Dysmorphic features or congenital malformations that adversely affect life expectancy or neurodevelopment;
- Unlikely to comply with long-term F/U;
- Prior treatment with a methylxanthine.

Groups:

- Caffeine ($n = 1,006$): Loading dose of 20mg/kg caffeine citrate, followed by daily maintenance of 5mg/kg. If apnoeas persisted, then daily maintenance increased to a maximum of 10mg/kg;
- Placebo ($n = 1,000$).

Primary endpoint: Combined rate of mortality and neurodevelopmental disability in survivors at a corrected age of 18mo.

Secondary endpoints: Rates of bronchopulmonary dysplasia, necrotizing enterocolitis, brain injury—intra- and periventricular haemorrhage, periventricular leukomalacia, and/or ventriculomegaly, and retinopathy of prematurity before discharge home. Growth failure until the corrected age of 18mo, and the functional status at 5y and 11–12y.

Other measures: Safety and efficacy.

Follow-up: Minimum 18mo F/U.

Results

Table 19.1 Summary of results

| Outcome | Caffeine | Placebo | Adjusted OR* | p |
|---------------------|-------------|-------------|--------------|-------|
| Composite | | | | |
| Death or disability | 377 (40.2%) | 431 (46.2%) | 0.78 | 0.008 |
| Components | | | | |
| Death before 18 mo | 62 (6.4%) | 63 (6.5%) | 0.98 | 0.87 |
| Cerebral palsy | 40 (4.4%) | 66 (7.3%) | 0.58 | 0.009 |
| Cognitive delay | 293 (33.8%) | 257 (20%) | 0.82 | 0.04 |
| Severe hearing loss | 17 (1.9%) | 22 (2.4%) | 0.77 | 0.41 |
| Bilateral blindness | 6 (0.7%) | 8 (0.9%) | 0.74 | 0.58 |

* OR was adjusted for gestational age, sex of the infant, the mother's education at the time of the assessment, antenatal administration of corticosteroids, and multiple births.

- A total of 69 (caffeine group) and 68 (placebo group) patients had inadequate data (see Table 19.1.)

Discussion

First drug treatment shown to reduce disability in the preterm infant. Further analysis of the secondary outcome measures is ongoing. Caffeine reduced the incidences of cerebral palsy and cognitive delay (defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development). No significant effects on the rates of death, severe hearing loss, or bilateral blindness were noted.

Problems

- Fixed caffeine dosing. Prior studies (*Pediatrics* (2002) 109, 784–7) suggested loading caffeine at similar levels reduced cerebral circulation. Subsequent studies (*Acta Paediatr* (2010) 99, 1319–23) suggest lower loading and maintenance doses are safer.
- Limited methodological information provided—no indication of which patients had escalation of maintenance dosing.
- A total of 2,309 not randomized: 1,628 lacked consent, 681 not approached (unspecified reasons), and 33 excluded for 'unknown reason'.

Perinatal asphyxial encephalopathy: hypothermia

TOBY (ToTal BodY Hypothermia for Neonatal Encephalopathy Trial) study group: Moderate hypothermia to treat perinatal asphyxial encephalopathy.

AUTHORS: Azzopardi D, Strohm B, Edwards D et al.

REFERENCE: *N Engl J Med* (2009) 361, 1349–58.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Induction of moderate hypothermia for 72h in term infants who had perinatal asphyxia did not significantly reduce the combined rate of death or severe disability, but did result in improved neurologically outcomes in survivors.

Impact

Early hypothermia is the only neuroprotective treatment for term newborn infants with asphyxial encephalopathy. This treatment is endorsed by the UK's NICE and other international guidelines.

Aims

Perinatal asphyxial encephalopathy is associated with high morbidity and mortality rates worldwide. Previous studies, such as CoolCap (Gluckman et al. *Lancet* (2005) 365, 663–70) and the National Institute of Child Health and Human Development (NICHD) (Shankaran et al. *N Engl J Med* (2005) 353, 1574–84), had shown no serious SEs to cooling; however, neither had sufficient power to assess neurodisability as a primary endpoint. This Total Body Hypothermia for Neonatal Encephalopathy Trial (TOBY) aimed to clarify this point.

Methods

Patients: 325 patients.

Inclusion criteria:

- Infants needed to sequentially fulfill criteria A, B, and C:
 - A. Infants ≥ 36 completed weeks' gestation admitted to the neonatal ICU (NICU) with at least one of: Apgar score of ≤ 5 at 10min after birth; continued need for resuscitation, at 10min after birth; pH < 7.00 within 60min of birth; or base deficit ≥ 16 mmol/L within 60min of birth;
 - B. Moderate to severe encephalopathy, consisting of altered state of consciousness (lethargy, stupor, or coma) AND at least one of: hypotonia; abnormal reflexes; absent or weak suck; or seizures;
 - C. At least 30min duration of abnormal background electroencephalographic (EEG) activity or seizures.

Exclusion criteria:

- Infants expected to be >6h of age at time of randomization;
- Major congenital abnormalities.

Groups:

- Intervention arm ($n = 163$): Intensive care plus passive and active cooling for 72h with a cooling blanket to target rectal temperature of 33–34°C, followed by rewarming at <0.5°C/h;
- Control arm ($n = 162$): Intensive care alone.

Primary endpoint: Combined incidence of mortality and severe neurodevelopmental disability in survivors.

Secondary endpoints: Included: intracranial and pulmonary haemorrhages, systemic hypotension, pulmonary HTN, sepsis, necrotizing enterocolitis, arrhythmia, duration of hospitalization, mortality, severe neurodevelopmental disability, multiple handicap, mental delay, epilepsy, cortical visual impairment, sensorineural hearing loss.

Other endpoints: Safety and efficacy of total body cooling.

Follow-up: Minimum 18mo F/U.

Results

- Intervention group: 42 infants died, and 32 survived with severe disability;
- Control group: 44 infants died, and 42 survived with severe disability (See Table 19.2.)

Table 19.2 Summary of results

| Primary endpoint | Cooling group | Non-cooled group | RR (95% CI) | <i>p</i> |
|---|---------------|------------------|------------------|----------|
| Combined death and severe neurodevelopmental disability | 74 (45%) | 86 (53%) | 0.86 (0.68–1.07) | 0.17 |
| Secondary endpoint | | | | |
| Survival without neurological abnormality | 71 (44%) | 45 (28%) | 1.57 (1.16–2.12) | 0.003 |

Discussion

The TOBY trial adds to the evidence from the CoolCap and NICHD trials, demonstrating that moderate hypothermia increases survival without disability. It is the only currently proven therapy for asphyxial encephalopathy, and its benefit has been confirmed subsequently in a Cochrane systematic review (Jacobs *et al. Cochrane Database Syst Rev* (2013) 1, CD003311). Even with hypothermia treatment, asphyxial encephalopathy remains a high morbidity and mortality condition for term babies.

Problems

- No effect on the primary endpoint.
- No data on premature or intrauterine growth-restricted babies.
- Cooling needs to be instituted within 6h of birth. Therefore, rapid access to a referral unit with appropriate equipment and skills is key to achieving benefit; this is not always available.

Cystic fibrosis: early diagnosis, growth and nutrition

Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth.

AUTHORS: Farrell P, Kosorok M, Laxova A et al. (Wisconsin Cystic Fibrosis Neonatal Screening Study Group).

REFERENCE: *Pediatrics* (2001) 107, 1–13.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Screening for cystic fibrosis (CF) at birth leads to early presymptomatic diagnosis and improved weight, height, and head circumference.

Impact

Newborn screening for CF now occurs in the USA, the UK, France, Australia, and New Zealand.

Aims

This paper aimed to determine whether early diagnosis of CF would be medically beneficial in terms of nutritional and growth outcomes, without major risk.

Methods

Patients: 650,341 of the total 657,630 births in Wisconsin from 1985 to 1994. All newborn babies had a dried blood trypsinogen level from 1985, and then from 1991 a gene assay (delta F508) was also used.

Exclusion criteria: Neonates with meconium ileus.

Groups:

- **Intervention ($n = 325,121$):** Those with a positive screening test were contacted and referred to one of the state CF diagnostic centres for a sweat test. F/U was standardized for all patients diagnosed with CF, with visits every 6wk for 1y and then every 3mo. Plasma levels of albumin, fat-soluble vitamins A and E, and essential fatty acids were measured at diagnosis and every 6mo. Prospective food charts were performed for 3d every 6mo;
- **Control ($n = 325,120$):** Notified of their result if the parents or physician requested, or at 4y of age, or after a diagnosis of CF was made.

Endpoints: Age, length, weight, head circumference centiles at diagnosis. Height or weight below 10th centile as index of malnutrition.

Follow-up: Concluded in 1998.

Results

- Of 657,630 births, 650,341 were randomized (99% of births);
- A total of 157 had a diagnosis of classical CF and one with probable CF with abnormal sweat test;
- Nine were diagnosed through unblinding/surveillance;
- A total of 195 parents in the control arm requested results (all negative);
- Five false negatives;
- A total of 77 infants diagnosed early in the screened group;
- A total of 81 children diagnosed later in the control group;
- Screened and control groups well balanced for birthweight, gender, parents education, ethnicity, and centre;
- Control group found to have fewer patients with pancreatic insufficiency and more with CFTR alleles other than delta F508;
- 92% F/U rate for visits for children with CF;
- OR for the risk of a weight below the 10th percentile in the control group, compared with the screened group, was 4.12 (95% CI 1.64–10.38), and the corresponding OR for height was 4.62 (95% CI 1.70–12.61). (See Table 19.3.)

Table 19.3 Summary of results

| Primary endpoint | Screened | Control | <i>p</i> |
|---|----------|---------|----------|
| Number with CF | 77 | 81 | – |
| Age at diagnosis (weeks) | 13 | 107 | <0.001 |
| Length at diagnosis (centile) | 44th | 26th | <0.001 |
| Weight at diagnosis (centile) | 35th | 25th | 0.027 |
| Head circumference at diagnosis (centile) | 52nd | 32nd | 0.003 |

Discussion

CF can be difficult to diagnose. Before screening was introduced, the average age of diagnosis was 4.8y. Children are often malnourished at the time of diagnosis. There were a large number of healthy infants screened for a relatively small pick-up rate; cost–benefit analysis will vary, depending on the wealth of the country. False positives may lead to anxiety, and false negatives may lead to false reassurance. The optimal screening strategy remains the subject of debate. Mortality, lung function, and developmental benefits are less clearly established. However, based on the nutritional benefits alone, many developed countries have integrated CF into their national newborn screening programmes.

Problems

- Relatively short F/U for a chronic condition.
- Ethical debate about the timing of unblinding for the control group.
- Use of anthropometrics as markers for morbidity or mortality outcomes.

Sudden infant death syndrome: sleeping position

Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002.

AUTHORS: Gilbert R, Salanti G, Harden M *et al.*

REFERENCE: *Int J Epidemiology* (2005) **34**, 874–87.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 3.

Key message

Despite there being sufficient data to show evidence of harm with the front sleeping position for infants from 1970, the delay in systematic analysis and translation to public health guidance is linked to 10,000 potentially preventable UK infants deaths and 50,000 across Europe, the USA, and Australasia.

Impact

The 'Back to Sleep' campaign that started in 1991 has led to a reduction in sudden infant death syndrome (SIDS) of between 50% and 70%.

Aims

This paper aimed to combine a systematic review and a meta-analysis of the effect of front and side sleeping on the risk of SIDS, with a historical review of recommendations on infant sleeping position in books and pamphlets on infant care available in the UK between 1940 and 2002.

Methods

Systematic review and meta-analysis: For the systematic review of clinical evidence of sleep position and SIDS, all case control or cohort studies were included that compared the risk of SIDS in infants sleeping on their front, side, or back. Studies had to be based on SIDS infants and live healthy control infants from the same community.

Historical review of advice to parents: The Modern Medicine Collection at the Wellcome Trust Library and the British Medical Association was searched for any book or pamphlet that referred to the care of normal-term infants aged <6mo and mentioned infant sleeping position. Dates reviewed were from 1940 to 2002. This was to assess the health advice being given to the public in the care of infants and sleep positioning.

Results

Risk of SIDS in relation to sleep position systematic review:

- A total of 2,897 abstracts scanned, 206 full-text articles retrieved, 40 studies met the inclusion criteria. No RCTs found;
- All 40 included studies provided data on front vs non-front positions, but only 24 studies separately recorded back and side positions;
- Of the 40 studies, 23 (and 15/24 reporting side and back positions) included some degree of matching of controls with cases;
- Of these, unadjusted matched ORs were available for 9/23 studies (and for 7/15 reporting side and back positions);
- For one study, derived pooled ORs from data reported for separate ethnic groups.

Historical review of parental advice:

- A total of 83 texts that met the inclusion criteria;
- From 1940 to the mid 1950s, all texts favoured the back or side positions, except for one;
- From 1954 until 1988, a substantial proportion of texts consistently favoured front sleeping, although many also favoured the side and back;
- No texts favoured the front position after 1988.
- By 1970, there were enough data to recommend the back was preferable to the front sleep position to prevent SIDS;
- By 1986, there were enough data to recommend the non-front was preferable to the front sleep position;
- It was not until 1992 the non-front sleep position for infants was advocated. (See Table 19.4.)

Table 19.4 Summary of results

| Risk of SIDS | OR | 95% CI |
|--------------------|------|-----------|
| Front vs back | 4.92 | 3.62–6.58 |
| Front vs non-front | 4.30 | 3.39–5.39 |

Discussion

The lag in analysis of data and translation to health advice had a profound negative effect on mortality. In this paper reviewing historical parental advice and a formal meta-analysis of published controlled trials, the authors illustrated the detrimental effect of not looking at the cumulative evidence. The risk of front sleeping could have been highlighted 15y earlier, leading to thousands of infant lives saved. This illustrates the importance of systematic reviews as part of the armoury of EBM.

Problems

- There was no RCT on sleep position.
- ‘Healthy adopter’ phenomenon probably led to bias, as those families with low risk of SIDS were those most likely to be following established health advice of the time.

Immunization: rotavirus vaccination

Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study.

AUTHORS: Vesikari T, Karvonen A, Prymula R *et al.*

REFERENCE: *Lancet* (2007) **370**, 1757–63.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A two-step vaccine provides high protection against ‘any’ and ‘severe’ rotavirus gastroenteritis, reducing admissions over two epidemic seasons.

Impact

Rotavirus vaccine has been introduced into international vaccination schedules, with primarily health economic benefits in developed countries and mortality benefits in developing countries.

Aims

Worldwide, an estimated 61,100 children die every year from rotavirus disease. The annual burden of rotavirus-related disease in Europe is estimated to account for over 200 deaths, 87,000 hospital admissions, and 700,000 outpatient visits in children below 5y. RotaShield®, a previous vaccine formulation, had an increased risk of intussusception and was withdrawn in 1999. This study aimed to investigate the efficacy of RIX4414 in Europe, at the titre level and composition corresponding to the licensed Rotarix® vaccine (an attenuated human monovalent vaccine), when administered alongside other vaccinations on the immunization programme, measured over two consecutive epidemic seasons.

Methods

Patients: 3,994 patients in Europe (Czech Republic, 299; Finland, 2,890; France, 146; Germany, 289; Italy, 25; Spain, 345).

Inclusion criteria:

- Healthy infants 6–14wk of age;
- Birthweight >2,000g (at the time of first study vaccination);
- Parent/guardians likely to comply with study protocol.

Exclusion criteria:

- Planned administration of a vaccine not foreseen by the study protocol;
- Immunosuppression, immunodeficiency, IV Ig or blood products;
- Chronic GI disease;
- Acute illness at the time of enrolment;
- Gastroenteritis within 7d preceding the first study vaccination;
- Clinically significant chronic illness.

Groups:

- RIX4114 vaccine ($n = 2,646$): 2,554 entered the second efficacy phase and continued with the trial. They received an oral vaccine, according to the schedule 0, 1, or 2mo at the same time as the first two oral doses of their childhood vaccines;
- Placebo ($n = 1,348$): 1,294 entered the second efficacy phase and continued with the trial. They received an oral substitute exact to the vaccine minus the virus component.

Primary endpoint: Occurrence of rotavirus gastroenteritis caused by the circulating wild-type rotavirus strains during first efficacy F/U period.

Secondary endpoint: Severe rotavirus gastroenteritis caused by circulating wild-type rotavirus strains (G1 and non-G1 serotypes), hospitalization, requiring medical attention during F/U.

Other endpoints: Safety and efficacy of the vaccine.

Follow-up: Minimum 18mo F/U.

Results

- Similar demographics (age, sex, race, height, weight).

Table 19.5 Summary of results

| | RIX4414 <i>n</i> (incidence: episodes/1,000 infants/y) | Placebo <i>n</i> (incidence: episodes/1,000 infants/y) | Vaccine efficacy, <i>p</i> % (95% CI) | |
|---|---|---|--|---------|
| Combined efficacy, two season F/U period (RIX4414, $n = 2,572$; placebo, $n = 1,302$) | | | | |
| Any severity | 85 (22.9) | 204 (108.1) | 78.9 (73–84) | <0.0001 |
| Severe | 24 (6.5) | 127 (67.3) | 90.4 (85–94) | <0.0001 |
| Admission | 2 (0.5) | 25 (13.2) | 96.0 (84–100) | <0.0001 |
| Medical attention | 41 (11.0) | 128 (67.8) | 84 (77–89) | <0.0001 |

Discussion

This and other papers have demonstrated this to be a safe and effective rotavirus vaccine, particularly in a developed world context. Rotarix® and RotaTeq® (a pentavalent human–bovine reassortant vaccine) have been widely endorsed by the WHO and USA's Center for Disease Control and Prevention. The health economic benefits seen in developed countries contrast with the mortality benefit seen in developing countries, despite lower vaccine efficacy (Richardson *et al.* *N Engl J Med* (2010) 362, 299–305). (See Table 19.5.)

Problems

- No health economic analysis.
- No vaccine comparison.

Maternal–infant transmission of HIV: zidovudine

Reduction of maternal–infant transmission of human immunodeficiency virus type-1 with zidovudine treatment.

AUTHORS: Connor E, Sperling R, Gelber R *et al.* (Pediatric AIDS Clinical Trials Group Protocol 076 Study Group).

REFERENCE: *N Engl J Med* (1994) 33, 1173–80.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Zidovudine given ante- and intrapartum to HIV-infected pregnant women, followed by 6wk treatment for the baby, reduces the risk of maternal-to-infant transmission of HIV type 1 (HIV T1) from 25.5% to 8.3%.

Impact

This landmark paper was the first major contribution to the package of care that now decreases mother-to-infant transmission of HIV to <1% where resources allow. The ability to prevent vertical transmission of HIV has been a major accomplishment of modern medicine.

Aims

Transmission of HIV T1 from affected mothers condemns children to either an incurable illness with high untreated morbidity and mortality, or complex medical management with high pill burden and SEs. The greatest transmission risk is in late pregnancy or during labour. Animal models showed zidovudine to prevent or alter the course of infection, with phase 1 studies demonstrating safety and appropriate placental drug carriage in pregnancy. This study assessed the safety and efficacy of this drug in preventing HIV transmission.

Methods

Patients: 477 pregnant women, at 59 centres in the USA and France, who gave birth to 415 live-born infants.

Inclusion criteria:

- Pregnant, HIV-infected women between 14 and 34wk gestation;
- CD4⁺ T-lymphocyte count >200 cells/mm³;
- No indication for ART (clinician judgement);
- Hb >8g/dL, absolute neutrophils >1,000/mm³, platelets >100,000 cells/mm³, ALT <2.5 upper limit of normal, creatinine >1.5mg/dL.

Exclusion criteria:

- Life-threatening fetal abnormality;
- Oligohydramnios (second trimester) or explained polyhydramnios (third);
- Fetal hydrops, ascites, or other evidence of fetal anaemia;

- Woman received: Any retroviral treatment in pregnancy, immunotherapy, anti-HIV vaccines, cytolytic chemotherapy, radiation;
- Newborn: Immediate life-threatening condition, hyperbilirubinaemia requiring treatment other than phototherapy, Hb <8, platelets <50, ALT 5× upper limit of normal. Received HIV vaccine or drug.

Groups:

- Zidovudine ($n = 239$): Mother—antepartum PO zidovudine 5× daily and intrapartum IV zidovudine (loading, then hourly until delivery); newborn—8–12h post-partum PO qds for 6wk;
- Placebo ($n = 238$).

Primary endpoint: Transmission rate of HIV T1 (one positive blood culture of peripheral blood mononuclear cells).

Secondary endpoint: Hb level, short-term toxic effects up to 78wk, maternal health effects, infant death, structural abnormalities (length, height, weight), safety, and efficacy.

Other measures: Safety and efficacy of zidovudine.

Follow-up: Infants evaluated frequently until 78wk of age.

Results

Table 19.6 Summary of results

| | Zidovudine | Placebo | Relative reduction in HIV vertical transmission |
|-----------------------------|----------------|------------------|---|
| % infected at 18mo (95% CI) | 8.3 (3.9–12.8) | 25.5 (18.4–32.5) | 67.5 (40.7–82.1; $p = 0.00006$) |

72wk estimates by the Kaplan–Meier Method.

At first interim analysis, enrolment discontinued, and all offered zidovudine.

- A total of 362 pregnancies yielding an infant for whom at least one result of HIV culture available (180 zidovudine group/183 placebo group);
- Only difference in secondary endpoints was lower Hb in the zidovudine group, which corrected by 12wk old. (See Table 19.6.)

Discussion

This and subsequent trials dramatically decreased the numbers of HIV-infected children where resources allowed. The European Mode of Delivery Collaboration study (*Lancet* (1999) 353, 1035–8) showed an 80% reduction in vertical transmission with pre-labour Caesarean section. Combinations of ART for mother and baby, obstetric management guided by viral load, time on treatment, medication adherence, obstetric factors, and the woman's views, and avoidance of breastfeeding can decrease transmission to <1% and enable vaginal deliveries (*HIV Med* (2012) 13(S2), 87–157).

Problems

- Introduction of viral load monitoring and initiation thresholds for ART, among others, have changed since this trial.
- Cannot determine when (second trimester to 6wk post-natal) is critical.
- Ethical debate about the use of placebo arms in trials following on from this study (see www.hks.harvard.edu/case/azt/ethics/).

Congenital cytomegalovirus: intravenous ganciclovir

Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial.

AUTHORS: Kimberlin D, Lin C-Y, Sanchez J, et al. (National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group).

REFERENCE: *J Pediatr* (2003) **143**, 16–25.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In infants ≤ 1 mo with clinically apparent CNS cytomegalovirus (CMV) disease, treatment with 6wk of IV ganciclovir prevents deterioration of hearing loss at 6mo, relative to no treatment.

Impact

Symptomatic newborns infected with CMV, including those with isolated sensorineural hearing loss, now receive IV ganciclovir as standard. This involves prolonged hospitalization and accompanying treatment-related risks of neutropenia and central venous access.

Aims

Congenital CMV infection is the commonest non-genetic cause of sensorineural hearing loss. Ten percent of congenitally infected fetuses are symptomatic at birth, with subsequent neurological sequelae in 90% and hearing deficit in 30–65% of cases. No effective antiviral therapy was available for congenital CMV infection. Following a phase 2 study of IV ganciclovir, this study aimed to evaluate the effect upon hearing of 6wk of IV ganciclovir in symptomatic CMV-infected neonates.

Methods

Patients: 100 patients at 17 centres in the USA.

Inclusion criteria: Infants ≤ 1 mo of age, ≥ 32 wk gestation, with birthweight $\geq 1,200$ g, with confirmed isolation of CMV from urine, and evidence of CNS involvement, including:

- Microcephaly;
- Intracranial calcifications;
- Abnormal CSF for age;
- Chorioretinitis; and/or
- Hearing deficits.

Groups:

- IV ganciclovir 6mg/kg bd for 6wk ($n = 25$);
- No treatment ($n = 17$). Placebo arm considered unethical due to maintaining IV access for 6wk.

Primary endpoint: Best-ear brainstem-evoked response (BSER) audiometry improvement by one gradation (e.g. moderate impairment at baseline and mild impairment at F/U) between baseline and 6mo F/U (or normal BSER at both time points).

Secondary endpoint: No deterioration in best-ear BSER audiometry between baseline and 6mo F/U.

Other endpoints: Laboratory (thrombocytopenia, hepatitis) and clinical (organomegaly, chorioretinitis) improvement, rate of growth, and death. Drug toxicity evaluated with full blood count (including neutrophil count), ALT, bilirubin, uric acid, and creatinine at ten time points in the treatment group and weekly in the no therapy group.

Follow-up: Minimum 6mo F/U.

Results

Table 19.7 Summary of results

| Primary endpoint | Ganciclovir | No therapy | OR (95% CI) | <i>p</i> |
|---|-------------|------------|----------------------|---------------------|
| Hearing improvement (or normal to normal) (6mo) | 21 (84%) | 10 (59%) | 5.03 (0.84–45.9) | 0.06 (adjusted) |
| Secondary endpoint | | | | |
| Hearing deterioration (6mo) | 0 (8%) | 7 (41%) | 21.11 (2.84 to ∞) | <0.01 (adjusted) |

Of 100 enrolled, sufficient data to evaluate primary endpoint only available for 25 (ganciclovir) and 17 (no therapy).

- 29/46 (63%) ganciclovir recipients developed grade 3 or 4 neutropenia, compared with 9/43 (21%) in the control group ($p < 0.01$);
- Of 29 ganciclovir-treated patients developing neutropenia, 14 required dose adjustments, and four had the drug permanently discontinued;
- Three babies had central venous catheter (CVC) infections. (See Table 19.7.)

Discussion

First and only RCT to compare ganciclovir to no treatment in CMV-infected symptomatic newborns. Despite potential bias from significant loss to F/U, it demonstrated a significant prevention in deterioration of hearing at 6mo, and potentially also 1y. Subsequent neurodevelopmental F/U data show less developmental delay with treatment (*J Clin Virol* (2009) **46** Suppl 4, S22–6). Subsequent guidelines (*Early Human Dev* (2011) **87**, 723–8) endorse IV ganciclovir for symptomatic CNS CMV disease in neonates, including those with isolated sensorineural hearing loss detected in newborn screening programmes. Risks remain of neutropenia and CVC-related complications. Ongoing research is exploring oral preparations (valganciclovir) and shorter treatment duration.

Problems

- Small numbers and large loss to F/U, with potential bias.
- Subanalysis by type of CNS disease (e.g. hearing loss only) not possible.

Kawasaki disease: addition of prednisolone

RAISE (Randomized controlled trial to Assess Immunoglobulin plus Steroid Efficacy for Kawasaki disease): Efficacy of immunoglobulin plus prednisolone for prevention of coronary artery abnormalities in severe Kawasaki disease: a randomised, open-label, blinded-endpoints trial.

AUTHORS: Kobayashi T, Saji T, Otani T et al.

REFERENCE: *Lancet* (2012) **379**, 1613–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In severe Kawasaki disease, addition of prednisolone to IVIG and aspirin decreased the absolute risk of coronary artery abnormalities by 20% and the need for additional therapy by 27%.

Impact

Forthcoming updated UK guidelines will now include steroids for cases of Kawasaki disease meeting specified severity criteria.

Aims

Previous studies of steroids for Kawasaki disease included high incidence of coronary artery abnormalities when used alone (*Pediatrics* (1979) **63**, 175–9), and no benefit with adding a single dose of pulsed IV methylprednisolone to conventional treatment (*N Engl J Med* (2007) **356**, 663–75). This study aimed to assess the efficacy of additional 1° prednisolone treatment for patients at high risk for non-response to 1° treatment with IVIG.

Methods

Patients: 248 patients at 74 hospitals in Japan.

Inclusion criteria:

- Kawasaki disease defined by Japanese diagnostic guidelines;
- Risk score for non-response to IVIG alone of >5.

Exclusion criteria:

- Previous history of Kawasaki disease;
- Diagnosed ≥9d after onset of fever;
- Pre-existing coronary artery abnormalities;
- Received steroids in last 30d or IVIG in last 180d;
- Concomitant severe medical disorders or suspected severe infection.

Groups:

- Intervention ($n = 125$): IVIG plus prednisolone (PSL) as control group plus prednisolone 2mg/kg/d by IV injection for 5d and oral when afebrile. Tapered once CRP low and H2 blocker also prescribed;
- Control ($n = 123$): IVIG 2g/kg over 24h and aspirin 30mg/kg/d until afebrile, followed by aspirin 3–5mg/kg/d for ≥28d after fever onset.

Primary endpoint: Coronary artery abnormalities in study period (2y).

Secondary endpoints:

- Incidence of coronary artery abnormalities at wk 4;
- Z-scores of coronary arteries;
- Incidence of need for additional rescue treatment;
- Serum concentrations of CRP at 1 and 2wk;
- Serious adverse events.

Follow-up: Two-dimensional (2D) echocardiogram (reviewed by paediatric cardiologists masked to patient identity and group assignment) and laboratory data at baseline, and wk 1, 2, and 4.

Results

Table 19.8 Summary of results

| | IVIG + PSL (n = 121) | IVIG (n = 121) | p |
|---|----------------------|----------------|---------|
| Coronary artery abnormality during study (%) | 4 (3%) | 28 (23%) | <0.0001 |
| Coronary artery abnormality at wk 4 (%) | 4 (3%) | 15 (13%) | 0.014 |
| Median duration of fever after enrolment in days (IQR) | 1 (1–1) | 2 (1–4) | <0.0001 |
| Non-response to 1° treatment requiring additional therapy | 16 (13%) | 48 (40%) | <0.0001 |
| Median CRP (mg/L) at wk 1 (IQR) | 2.5 (1–5) | 6 (4–13) | <0.0001 |

Discussion

In severe cases of Kawasaki disease with a high risk of no response to initial treatment with IVIG, addition of prednisolone leads to a dramatic decrease in coronary artery abnormalities and the need for rescue therapy, as well as fever duration and inflammatory markers. Forthcoming UK guidelines will incorporate steroids if specific criteria are met, following this trial. (See Table 19.8.)

Problems

- No placebo; therefore, treating physicians and families not blinded.
- Findings apply exclusively to severe cases (71% excluded for low risk).
- No comment on the degree of clinical risk with coronary artery abnormalities.
- Unclear how evidence is applicable to non-Japanese populations.

Virus-induced wheeze: prednisolone

Oral prednisolone for preschool children with acute virus-induced wheezing.

AUTHORS: Panickar J, Lakhanpaul M, Lambert PC et al.

REFERENCE: *N Engl J Med* (2009) **360**, 329–38.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In children less than 5 years old with mild to moderate viral-induced wheeze, oral prednisolone does not shorten the duration of hospitalization, severity scores, or readmission rates, even in children at risk of atopic asthma.

Impact

Prescription of oral steroids following admission in such mild to moderate cases is falling out of favour due to the findings of this study.

Aims

Virus-induced wheeze is one of the commonest paediatric presentations in preschool-aged children in the Western world. The use of systemic corticosteroids, in addition to bronchodilators and O₂, in these children is controversial, with conflicting evidence as to their efficacy. This double-blind, placebo-controlled RCT aimed to assess the efficacy of a short course of oral prednisolone in children presenting to a hospital with virus-induced wheezing.

Methods

Patients: 687 patients enrolled at three UK centres from 2005 to 2007.

Inclusion criteria: Children referred to hospital or attending the ED, aged between 10mo and 60mo, with an attack of wheezing that the physician judged to be preceded by signs and symptoms of a viral upper respiratory tract infection.

Groups:

- Prednisolone ($n = 343$): 5d course of 10mg od for children aged 10–24mo, 20mg od for older children;
- Placebo ($n = 344$).

Primary endpoint: Duration of hospitalization, i.e. time from enrolment to actual discharge and to time patient being 'fit for discharge'.

Secondary endpoint: Preschool respiratory assessment measure (PRAM) scores at 4, 12, and 24h; total dose of inhaled salbutamol (albuterol) in hospital; mean parent-assessed symptom score and salbutamol actuations delivered in following 7d; time to be 'back to normal'; and hospital readmission for wheezing within 1mo of discharge.

Prespecified subgroup analysis: Children at increased risk of atopic asthma (history of four or more wheezing episodes who had a parent with asthma or who had physician-diagnosed eczema).

Results

Table 19.9 Summary of results

| Primary endpoint: median duration of hospitalization | Oral prednisolone | Placebo | p |
|--|-----------------------|-----------------------|----------------------|
| From presentation to sign-off for discharge (h) | 10.1 (n = 340) | 12.0 (n = 342) | 0.16 |
| From presentation to actual discharge (h) | 11.0 (n = 341) | 13.9 (n = 343) | 0.18 |
| Secondary endpoints | Oral prednisolone | Placebo | Difference (95% CI) |
| PRAM score at 12h | 2.49 ± 1.98 (n = 149) | 2.28 ± 2.03 (n = 163) | 0.20 (−0.24 to 0.64) |
| Hospital readmission for wheezing within 1mo | 21/283 (7.4%) | 19/303 (7.4%) | – |

- No significant difference in the secondary outcomes was identified.
- A total of 124 children (58 in the placebo group and 66 in the prednisolone group) classified as being at high risk for asthma, and, in a prespecified subgroup analysis, there was no difference in the primary outcome nor evidence of a differential treatment effect. (See Table 19.9.)
- One family in the prednisolone group attributed excess vomiting to the study group and was discontinued after discharge.

Discussion

This high-quality trial provides evidence to guide the management of one of the commonest paediatric presentations to 2° care. Being conducted at three UK sites means the population is comparable to those attending EDs or referred by 1° care. Oral steroid administration to children with wheeze has, for too long, been a reflex, without consideration of the significant SEs, including sleep and appetite disturbances, following short-term administration. The subgroup analysis shows that even those children at risk of developing atopic asthma at school age do not benefit from steroids, decreasing the temptation to prescribe by the physician.

Problems

- Baseline PRAM scores were measured after initial bronchodilator administration and therefore did not reflect the maximum severity of wheezing at presentation.
- Information not available on the 318 families who declined to participate from the 1,180 assessed for eligibility.

Resuscitation of the sick child: fluids boluses in Africa

FEAST (Fluid Expansion As Supportive Therapy) study: Mortality after fluid bolus in African children with severe infection.

AUTHORS: Maitland K, Kiguli S, Opoka R et al.

REFERENCE: *N Engl J Med* (2011) **364**, 2483–95.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Contrary to previous dogma, administration of fluid boluses to children with impaired perfusion at presentation significantly increases 48h mortality in an African setting from 7.3% to 10.5%.

Impact

WHO guidelines on hospital management of the sick child are under review, and research into fluid resuscitation is expanding rapidly to examine the implications for other contexts.

Aims

Rapid fluid boluses for the shocked child in the developed world are the mainstay of resuscitation guidelines. The benefit in developing countries with different pathologies and less access to intensive care was unclear. The FEAST study was designed to compare early resuscitation with a saline bolus with no bolus and an albumin bolus.

Methods

Patients: 687 patients enrolled at three African centres from 2005 to 2007.

Inclusion criteria:

- Age 60d to 12y;
- Severe febrile illness with impaired consciousness and/or respiratory distress plus impaired perfusion (capillary refill time >3s, lower limb temperature gradient, weak radial pulse volume, severe tachycardia).

Exclusion criteria:

- Severe malnutrition, gastroenteritis, non-infectious shock (e.g. trauma/burns/surgery).

Groups:

- Stratum A—without severe hypotension:
 - Saline bolus group: 20mL/kg over 1h;
 - Albumin bolus group: 20mL/kg over 1h;
 - Control: No bolus;
- Stratum B—severe hypotension:
 - Saline bolus group: 40mL/kg over 1h ($n = 16$);
 - Albumin bolus group: 40mL/kg over 1h ($n = 13$).

All (except no bolus) received further 20mL/kg, if persistent impaired perfusion. All received further 40mL/kg, if severe hypotension developed. June 2010 amendment—initial bolus increased to 40mL/kg (A) and 60mL/kg (B). All received standard care, including maintenance fluids and 10mL/kg blood transfusion, if Hb <5g/dL.

Primary endpoint: Mortality 48h after randomization.

Secondary endpoint: 4wk mortality; neurologic sequelae at 4 and 24wk; hypotensive shock in 48h of randomization; adverse events (pulmonary oedema, raised intracranial pressure (ICP), severe allergic reaction).

Results

Table 19.10 Summary of results

| Endpoints | Albumin or saline bolus (%) (n = 2,097) | No bolus (%) (n = 1,044) | Any bolus vs no bolus, RR (95% CI) | p |
|---|--|-----------------------------|------------------------------------|-------|
| 48h mortality | 221 (10.5) | 76 (7.3) | 1.45 (1.1–1.9) | 0.003 |
| 48h pulmonary oedema, raised ICP, or both | 50 (2.4) | 17 (1.6) | 1.46 (0.85–2.5) | 0.17 |
| 4wk mortality | 254 (12) | 91 (8.7) | 1.39 (1.1–1.7) | 0.004 |
| 4wk neurologic sequelae | 295/1,986 (14.9) | 111/997 (11.1) | 1.33 (1.1–1.6) | 0.005 |

- Enrolment stopped early by independent data and safety monitoring;
- No significant difference between saline and albumin boluses;
- Subgroup analyses showed the difference in mortality was unrelated to anaemia, malaria, severity of acidosis, or elevated lactate. (See Table 19.10.)

Discussion

This paper challenges one of the fundamental tenets of care of the sick child. The clear evidence of harm with fluid boluses in the African setting triggered much debate and an explosion of interest in fluid management. It was awarded the *BMJ* Paper of the Year 2012.

Problems

- Shock difficult to reliably define in these settings, although the effect held true when analysed by multiple different clinical criteria.
- Hypovolaemic shock from dehydration or blood loss excluded; therefore, findings cannot be applied to these or dengue shock.
- No bolus group received blood transfusion earlier.

Part 4

Surgical specialties

Anaesthetics

- Introduction 538
- Preoperative cardiopulmonary exercise testing 540
- Traumatic bleeding: tranexamic acid 542
- WHO safe surgery checklist 544
- Laryngoscopy: use of cricoid pressure 546
- Depth of anaesthesia: bispectral monitoring 548
- Safety of epidural analgesia 550
- Reversal of neuromuscular block by sugammadex 552
- Enhanced recovery following major abdominal surgery 554
- Post-operative nausea and vomiting 556

Introduction

Anaesthesia has evolved significantly since its introduction in the 1840s, which transformed surgical practice and patient care. Early advances in safety came with the introduction of improved inhalational agents, along with local anaesthetic agents such as cocaine. This enabled surgery to be undertaken, using a balance of drugs with quite different properties, and introduced new techniques in the 1900s such as epidural and spinal anaesthesia. Further developments followed, including the introduction of endotracheal intubation to provide more secure control of the airway and breathing, IV drugs to permit induction of anaesthesia, and muscle relaxants to allow neuromuscular blockade in a controlled and reversible manner.

Current anaesthetic practice is provided, using a combination of many different available techniques and drugs, with the 1° aim of ensuring patient safety and high-quality care is provided for patients of any age, often with significant co-morbidities and requiring increasingly complex surgical interventions. Increased possibilities for the provision of day surgery have become possible due to more rapid and reliable recovery from anaesthesia associated with fewer complications such as post-operative nausea or sedation.

Anaesthesia as a profession has also expanded to provide patient care in many different environments and circumstances beyond the operating theatre. Anaesthetists are commonly consulted in the preoperative period to ensure patients being scheduled for surgery are optimized, with care continuing post-operatively in the high dependency unit (HDU) or ICU. Anaesthetists are frequently involved in care of patients in the labour suite, EDs, during interhospital transfers of critically ill patients, and on the wards for acute pain management. The advent of chronic pain management has also been led by anaesthetic practitioners and now forms an area of specialist practice in its own right.

Anaesthesia today is extremely safe, with mortality of <1 in 250,000 directly related to anaesthetic intervention alone. This is due to a continued focus on the principles of patient safety and quality of care, underpinned by continued innovation in pharmacology, applied physiology, physics, and engineering. These have yielded improved techniques and technologies to enhance airway management, provide ventilatory assistance and haemodynamic support, and monitor physiological parameters. As a profession, anaesthesia has led in the development of standards, the use of audit, and the development of the concepts of clinical governance. Modern professional practice is continually seeking to improve by emphasizing the importance of individual non-technical skills in educational curricula and the workplace. In addition, anaesthetists are heavily involved in the integration of human factors science into health-care organizations.

Preoperative cardiopulmonary exercise testing

Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly.

AUTHORS: Older P, Hall A, Hader R.

REFERENCE: *Chest* (1999) **116**, 355–62.

STUDY DESIGN: Prospective consecutive series.

EVIDENCE LEVEL: 2a.

Key message

In elderly patients scheduled to undergo major intra-abdominal surgery, preoperative cardiopulmonary exercise (CPX) testing to quantify the anaerobic threshold (AT) can help identify patients at high risk for perioperative mortality, and hence influence perioperative medical management.

Impact

The ability to better predict perioperative mortality and morbidity prior to major surgery allows those in higher-risk cohorts to be counselled effectively and for their perioperative management and post-operative critical care support to be planned in advance. This allows available resources to be managed more efficiently, while improving patient experience and safety.

Aims

CPX testing yields a wealth of data on patient physiology and response to exercise (or increased metabolic demand). To develop an integrated strategy for the identification and subsequent management of high-risk elderly patients scheduled for major intra-abdominal surgery, in order to reduce both perioperative morbidity and mortality.

Methods

Patients: 702 patients (over 3y period).

Inclusion criteria: Aged >60y (or <60y with ischaemic heart disease or cardiac failure) for major abdominal surgery.

Exclusion criteria: Thoracic surgery ($n = 82$) and did not proceed to have surgery ($n = 72$).

Primary endpoints: Perioperative surgical mortality (i.e. during admission) due to cardiopulmonary complications. Early (death occurring <10d of surgery) or late (≥ 10 d) mortality.

Secondary endpoints: Perioperative mortality from other factors (including progression of disease, surgical or anaesthetic misadventure, or other miscellaneous causes).

Groups: Patients underwent preoperative CPX screening in the 2wk preceding admission to calculate their individual AT and also to identify significant new ST-depression on 12-lead continuous ECG during the test. This data, combined with the type of surgery planned, was used to assign patients into:

- ICU: AT <11mL/min/kg, or scheduled for aortic or oesophageal surgery ('high-risk'). Admitted to ICU pre- and post-operatively for invasive haemodynamic monitoring (pulmonary artery catheter, PAC), and optimization of fluid and haemodynamic status;
- HDU: AT >11mL/min/kg, but with either myocardial ischaemia or pulmonary dysfunction (CPX criteria of ventilator equivalent for O₂, Ve/VO₂ >35). Had invasive haemodynamic monitoring (central venous and arterial pressure cannulae) intraoperatively and admitted to HDU post-operatively for close attention and intensive physiotherapy;
- Ward-based: Remaining; no additional special measures during the perioperative period.

Results

- Age >60y (*n* = 476); age <60y but known ischaemic heart disease/ cardiac failure (*n* = 72). (See Table 20.1.)

Table 20.1 Summary of results

| AT <11mL/min/kg or aortic/oesophageal surgery | AT >11mL/min/kg with myocardial ischaemia or Ve/VO ₂ >35 on CPX | AT >11mL/min/kg with no myocardial ischaemia and Ve/VO ₂ <35 on CPX |
|---|--|--|
| ICU group | HDU group | Ward group |
| 28% (<i>n</i> = 153) | 21% (<i>n</i> = 115) | 51% (<i>n</i> = 280) |
| CVS mortality | CVS mortality | CVS mortality |
| 4.6% (<i>n</i> = 7) | 1.7% (<i>n</i> = 2) | 0% |

Discussion

This screening tool helped stratify patients according to their perioperative CV mortality risk, allowing prospective decisions to be made regarding required levels of perioperative critical care. CPX testing is relatively simple to perform, although it requires access to suitable facilities and some expertise. Due to increased demands on limited critical care resources, this offers a useful adjunct to existing systems and protocols to help plan perioperative care for high-risk patient populations.

Problems

Need to identify the most appropriate data sets to improve the predictive capability, to determine its value in other cohorts, and to evaluate factors to be optimized preoperatively to reduce CV mortality.

Traumatic bleeding: tranexamic acid

Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial.

AUTHORS: Roberts I, Perel P, Prieto-Merino D et al.

REFERENCE: *BMJ* (2012) 345, e5839.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The beneficial effects of tranexamic acid in reducing all-cause mortality and deaths from bleeding in patients with traumatic bleeding do not seem to vary significantly by baseline risk of death.

Impact

Tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and should not be restricted to the most severely injured.

Aims

The CRASH-2 trial (*Lancet* (2010) 376, 23–32) identified that a short course of tranexamic acid given within 3h of injury to adult patients with traumatic bleeding significantly reduced all-cause mortality, with no apparent increase in the risk of adverse thrombotic events. However, there was no differentiation between low- and high-risk groups. A benefit in the high-risk group may have hidden a detrimental effect in the low-risk group. This study involved prespecified analyses of the CRASH-2 trial data to examine how effects of treatment with tranexamic acid varied, based on the baseline risk of death in patients with traumatic bleeding.

Methods

Patients: 13,273 trauma patients from multiple UK centres.

Inclusion criteria: Patients with traumatic bleeding, treated with tranexamic acid or placebo within 3h of injury (CRASH-2).

Primary endpoint: All-cause mortality.

Secondary endpoints: Death from bleeding. Thrombotic events (fatal and non-fatal MI, stroke, DVT, and PE).

Groups: Grouped by risk of mortality (<6%, 6–20%, 21–50%, >50%).

Results

- Deaths from all causes in patients with traumatic bleeding, according to treatment with tranexamic acid ($p = 0.96$ for heterogeneity);
- Death from bleeding in patients with traumatic bleeding, according to treatment with tranexamic acid ($p = 0.98$ for heterogeneity). (See Tables 20.2 and 20.3.)

Table 20.2 Summary of results

| Risk of death at baseline | No of patients (%) | | OR |
|---------------------------|--------------------|----------------|------------------|
| | Tranexamic acid | Placebo | |
| <6% | 14/2,487 (1%) | 21/2,353 (1%) | 0.63 (0.32–1.24) |
| 6–20% | 96/2,682 (4%) | 134/2,713 (5%) | 0.71 (0.55–0.93) |
| 21–50% | 98/908 (11%) | 142/940 (15%) | 0.68 (0.53–0.88) |
| >50% | 106/607 (17%) | 132/583 (23%) | 0.72 (0.56–0.93) |
| All | 314/6,684 (5%) | 429/6,589 (7%) | 0.71 (0.61–0.82) |

Table 20.3 Summary of results

| Risk of death at baseline | No of patients (%) | | OR |
|---------------------------|--------------------|----------------|------------------|
| | Tranexamic acid | Placebo | |
| <6% | 14/2,487 (1%) | 21/2,353 (1%) | 0.63 (0.32–1.24) |
| 6–20% | 96/2,682 (4%) | 134/2,713 (5%) | 0.71 (0.55–0.93) |
| 21–50% | 98/908 (11%) | 142/940 (15%) | 0.68 (0.53–0.88) |
| >50% | 106/607 (17%) | 132/583 (23%) | 0.72 (0.56–0.93) |
| All | 314/6,684 (5%) | 429/6,589 (7%) | 0.71 (0.61–0.82) |

Discussion

The beneficial effects of tranexamic acid in reducing all-cause mortality and deaths from bleeding in patients with traumatic bleeding do not seem to vary significantly by baseline risk of death. Tranexamic acid reduced the odds of death from bleeding by about 30% in each of the baseline risk strata studied, and reduced the odds of thrombotic events by about 30%. This reduction did not vary significantly by baseline risk of death. Taken together, these data suggest that tranexamic acid can be administered safely to a wide spectrum of patients with traumatic bleeding and that its use should not be restricted to those with the most severe haemorrhage. Absence of evidence of heterogeneity by baseline risk of death, however, should not be taken as evidence of absence. In particular, in the lowest-risk group, the precision of the estimated effect is low, and there remains some uncertainty.

Problems

- Results based on a subgroup analysis should be interpreted cautiously. However, the main trial showed a reduction in the risk of fatal and non-fatal MI and fewer thrombotic events with tranexamic acid (treated up to 8h after injury).
- Establishing the cause of death in trauma patients can be difficult, and any inaccuracy might have affected the estimate of the effect of tranexamic acid on fatal thrombotic events. Diagnostic inaccuracy, however, tends to obscure treatment effects and would not readily explain the observed reduction in thrombotic events with tranexamic acid.

WHO safe surgery checklist

A surgical safety checklist to reduce morbidity and mortality in a global population.

AUTHORS: Haynes A, Weiser T, Berry W *et al.*

REFERENCE: *N Engl J Med* (2009) **360**, 491–9.

STUDY DESIGN: Prospective study, pre and post intervention.

EVIDENCE LEVEL: 2b.

Key message

Checklists can prevent large numbers of deaths and disabling complications, and should be applied on a local and global basis.

Impact

The use of checklists can significantly reduce the rate of complications and deaths in the surgical patient population. Although this study looks at 'surgical' checklists, anaesthetists are an essential part of the team utilizing the checklist, and many of the aspects considered often fall under the anaesthetic remit, e.g. pulse oximetry monitoring, anticipated difficulty with airway management, prophylactic antibiotic administration, IV access, use of patient warming, and intraoperative glycaemic control.

Aims

In 2008, the WHO published guidelines identifying multiple recommended practices to ensure the safety of surgical patients worldwide. On the basis of these guidelines, a 19-item globally applicable checklist was developed to reduce the rate of major surgical complications. The study group hypothesized that implementation of this checklist and the associated culture changes it signified would reduce the rates of death and major complications after surgery in diverse settings.

Methods

Patients: 3,733 patients during baseline period, and 3,955 patients after checklist implementation (500 consecutive patients at each of eight hospital sites over a period of <3mo for each of the two phases of the study).

Inclusion criteria: Age >16y.

Primary endpoints: Any major complication, including death, during the period of post-operative hospitalization, up to 30d.

Secondary endpoints: ARF; bleeding (requiring >4U of red cells in the first 72h); cardiac arrest (requiring cardiopulmonary resuscitation); coma (>24h); DVT; MI; unplanned intubation; ventilator use (>48h); pneumonia; PE; stroke; major disruption of wound; infection of surgical site; sepsis; septic shock; SIRS; unplanned return to the operating room; vascular graft failure; death.

Safety points assessed (covered within checklist): Objective evaluation and documentation of patients' airway prior to anaesthesia; use of pulse oximetry; IV access $\times 2$ or CVC if $>500\text{mL}$ of anticipated blood loss; prophylactic antibiotics within 60min before incision (with exceptions); oral confirmation of patient identity, operative site, and procedure; completion of sponge count at end of procedure.

Results

- Outcomes before vs after checklist implementation (see Table 20.4);
- Overall compliance with the six safety measures increased from 34.2% to 56.7% with the introduction of the checklist.

Table 20.4 Summary of results

| Surgical site infection | Unplanned return to operating room | Pneumonia (%) | Death | Any complication |
|-------------------------|------------------------------------|---------------|-------|------------------|
| <0.001 | 0.047 | 0.46 | 0.003 | <0.001 |

Discussion

The introduction of the WHO Surgical Safety Checklist into operating rooms at eight diverse hospitals globally was associated with marked improvements in surgical outcomes. Post-operative complications and death fell by similar amounts. The three sites with the most significant reductions were in one high-income and two low-income areas, suggesting local affluence does not affect the results. The reduction in complications was maintained when adjusted for case-mix variables and single-site effect. Although some of the biggest results were in pulse oximetry use, which may already be adhered to within the west, the results with antibiotic administration and oral confirmation of patient identity, site, and procedure are applicable to all.

Problems

- The group acknowledge many limitations, including 'The Hawthorne effect'—improvement in subject performance due to the knowledge of being observed, which may have skewed the results from this study.
- Unable to randomly assign the use of the checklist to operating rooms without risk of cross-contamination.
- Unable to allow for secular trends, although they did try to make allowances for this; however, individual culture may affect adherence and success of checklists on a day-to-day basis.

Laryngoscopy: use of cricoid pressure

The effect of cricoid pressure and neck support on the view at laryngoscopy.

AUTHORS: Vanner R, Clarke P, Moore W *et al.*

REFERENCE: *Anaesthesia* (1997) 52, 896–913.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Cricoid pressure provides improved views at laryngoscopy, particularly if applied upwards and backwards.

Impact

Correctly applied cricoid pressure can usually improve poor laryngoscopic views, facilitating easier intubation.

Aims

Cricoid pressure is routinely used during ‘crash’ induction to prevent regurgitation of gastric contents (i.e. in emergency cases with patients who have not been starved). However, some reports indicate that it may make tracheal intubation more difficult and that there is a lack of evidence to substantiate the use of adjunct techniques, including foam neck support and bimanual cricoid pressure. This study aimed to investigate the views at laryngoscopy, with and without application of cricoid pressure, as well as views obtained with standard upward pressure vs backward and upward pressure.

Methods

Patients: 50 patients at one centre in the UK.

Inclusion criteria:

- ♀;
- Not pregnant;
- Gynaecological operation requiring tracheal intubation.

Exclusion criteria:

- CV disease;
- Symptoms of reflux.

Conditions:

- Six conditions: no cricoid pressure, standard cricoid pressure, and upward and backward cricoid pressure, all with and without neck support;
- Larynx view grading 1–3, as proposed by Cormack and Lehane (*Anaesthesia* (1984) 39, 1105–11). Grade 1 represents a better view of the glottis; grade 3 represents no clear views of the glottis.

Results

- Results with and without neck support = no significant difference.
- Laryngoscopy view: $p = 0.02$ (not significant, as inadequate grade 2/3 views for chi-square or other statistical tests to be valid). (See Tables 20.5 and 20.6.)

Table 20.5 Summary of results (1)

| (With neck support) | Laryngoscopy view | | | p (of best view) |
|------------------------------|-------------------|---|---|--------------------|
| | 1 | 2 | 3 | |
| No pressure | 44 | 5 | 1 | 6% (CI 2–12%) |
| Upward and backward pressure | 50 | 0 | 0 | 44% (CI 34–54%) |
| Standard pressure | 48 | 2 | 0 | 11% (CI 6–19%) |

Table 20.6 Summary of results (2)

| | Best view | | Best view |
|-------------------|---|---------------|---|
| Up and back | $n = 51$ | With support | $n = 9$ |
| Standard pressure | $n = 13$ | No support | $n = 20$ |
| No difference | $n = 36$ | No difference | $n = 21$ |
| CONCLUSION | Up and back better than standard ($p < 0.01$) | CONCLUSION | No significant difference ($p = 0.1$) |

Discussion

This study formally confirmed what was anecdotally noted by most anaesthetists in practice—correctly applied cricoid pressure of optimal force helps improve poor laryngoscopy views. Backward and upward pressure gave better views than standard cricoid pressure. However, there was no significant improvement obtained by the use of a supporting neck pillow. Note that this technique is very ‘UK and colonies’-specific. In most anaesthetists’ minds, the Sellick manoeuvre remains the optimal technique (*Lancet* (1961) 2, 404–6).

Problems

- Potential for observer bias (as it was not possible to blind a study of this nature).
- Small numbers.

Depth of anaesthesia: bispectral monitoring

B-Aware!: Bispectral index monitoring to prevent awareness during anaesthesia.

AUTHORS: Myles P, Leslie K, McNeil J et al.

REFERENCE: *Lancet* (2004) **363**, 1757–63.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Using bispectral index (BIS) monitoring in high-risk patients reduces the incidence of awareness under anaesthesia.

Impact

BIS monitoring should ideally be used for high-risk anaesthesia to prevent patient awareness of the procedure. Cost and other resource issues persist in limiting its adoption into mainstream practice in the UK; however, medico-legal considerations related to the detection of intraoperative awareness have led to its wider use in some populations (e.g. the USA and Australia).

Aims

Awareness under anaesthesia is a distressing complication, quoted to occur in <0.2% of surgical patients. Incidence is reportedly higher during Caesarean section and cardiac/trauma surgery. Although depth of anaesthesia is classically monitored by clinical measures, including BP and HR, these are unreliable. BIS monitoring involves time and frequency domain, and bispectral analysis of the EEG. This trial aimed to assess whether BIS could reduce the incidence of awareness under anaesthesia.

Methods

Patients: 2,463 patients at multiple centres in Australia and New Zealand.

Inclusion criteria:

- Age ≥ 18 y, undergoing relaxant general anaesthesia;
- ≥ 1 risk factor for awareness:
 - Caesarean section, high-risk cardiac surgery (EF <30%, cardiac index <2.1L/min/m², severe aortic stenosis, pulmonary HTN, undergoing off-pump CABG surgery), acute trauma with hypovolaemia, rigid bronchoscopy, significant impairment of CV status and expectant intraoperative hypotension, severe end-stage lung disease, history of awareness, anticipated difficult intubation, known/suspected heavy alcohol intake, chronic benzodiazepine/opiate use, current protease inhibitor use.

Exclusion criteria:

- Traumatic brain injury, memory impairment, or psychosis;
- Known EEG abnormality.

Groups:

- BIS monitoring ($n = 1,225$);
- Control ($n = 1,238$).

Primary endpoint: Patient-confirmed awareness under anaesthesia at any time (structured questionnaire).

Secondary endpoints:

- Possible awareness;
- Recovery time;
- Hypnotic drug administration;
- Marked hypotension (SBP < 90 mmHg requiring drug treatment);
- Anxiety and depression (hospital anxiety and depression validated scale);
- Patient satisfaction (1–5 scale, at 30/7);
- Major complications;
- 30d mortality.

Follow-up: Post-operative interviews at 2–6h, 24–36h, and 30d.

Results

Table 20.7 Summary of results

| Primary endpoint | BIS ($n = 1,225$) | Control ($n = 1,238$) | p |
|--------------------------------------|---------------------|-------------------------|-----------------|
| Awareness | 2 (0.2%) | 11 (0.9%) | 0.02 |
| Secondary endpoints | | | |
| Possible awareness | 22 (1.8%) | 27 (2.2%) | 0.5 |
| Recovery time | 63 (40–95) min | 66 (40–100) min | 0.3 |
| Hypnotic drug given | 91 (7%) | 80 (6%) | 0.3 |
| Marked hypotension | 717 (58%) | 694 (56%) | 0.2 |
| Anxiety (A) and depression (D) score | 3 and 3 | 3 and 3 | 1.0 A; 0.7 D |
| Patient 'very satisfied' | 751 (67%) | 781 (68%) | 0.5 |
| Major complications | 283 (23.2%) | 288 (23.4%) | 0.9 |
| Mortality at 30d | 51 (4.2%) | 50 (4.1%) | 0.9 |

Discussion

A well-designed trial with a very specific primary outcome. Reduction in awareness was the only positive trial outcome. The NNT to prevent one episode of awareness in high-risk patients was 138. (See Table 20.7.)

Problems

- Only patients at high risk for awareness were included; the cost of using a BIS monitor for all patients may not be justified. However, this must be balanced against the considerable cost of awareness.

Safety of epidural analgesia

MASTER (Multicentre Australian Study of EpiduRal anaesthesia) trial: Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial.

AUTHORS: Rigg J, Jamrozik K, Myles P et al. (MASTER Study Group).

REFERENCE: *Lancet* (2002) **359**, 1276–82.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Epidural anaesthesia does not affect post-operative mortality or major complication rates, but does decrease respiratory complications.

Impact

Epidural anaesthesia as post-operative analgesia for high-risk patients has the desirable potential of reducing respiratory complications, a factor that may improve post-operative recovery.

Aims

The benefits of epidural analgesia have been long debated. While it can reduce the perioperative stress response, epidural catheter insertion is not without its risks. This trial aimed to compare outcomes in high-risk patients in whom epidural anaesthesia or alternative regimes had been used for post-operative analgesia.

Methods

Patients: 888 patients, at 25 centres in six countries (Australia, East Asia, and the Middle East).

Inclusion criteria:

- High-risk patients, i.e. ≥ 1 risk factor for adverse events:
 - Morbid obesity, DM, chronic renal failure, respiratory insufficiency, major hepatocellular disease, cardiac failure, acute MI, myocardial ischaemia, or age ≥ 75 , and ≥ 2 of: significant respiratory disease, cardiac dysrhythmia, HTN, moderate obesity, frailty, previous MI;
- Elective non-laparoscopic surgery of the abdomen or oesophagectomy;
- Operations lasting > 1 h.

Exclusion criteria:

- Cardiac or pulmonary surgery;
- Age < 18 y;
- Patients undergoing surgery within 12h of admission to hospital;
- Contraindications for epidural insertion.

Groups:

- Epidural group ($n = 461$). Only 225 fully compliant with protocol of 72h of post-operative epidural analgesia;
- Control group ($n = 454$).

Primary endpoint: Combined endpoint of mortality or major post-operative complication within 30d.

Secondary endpoint: Visual analogue pain score.

Results

Table 20.8 Summary of results

| | Control | Epidural | <i>p</i> |
|---|--------------|--------------|----------|
| Combined endpoint | 60.7% | 57.1% | 0.3 |
| Respiratory failure | 30.2% | 23.3% | 0.02 |
| 10cm visual analogue pain score (after coughing, morning of d 3) | 3.5 (SD 2.6) | 2.8 (SD 2.5) | 0.0007 |

Discussion

Although no difference in mortality or major post-operative complication rate was demonstrated in this study, the post-operative respiratory failure rate was less in the epidural group. This was supported by lower pain scores in patients having epidural analgesia, which allowed better physiotherapy, deep breathing, and coughing to be performed post-operatively. Although this study demonstrated a non-significant benefit for the defined primary endpoint of mortality or major complication within 30d, it is reassuring to know that epidurals do decrease respiratory complications. (See Table 20.8.)

Problems

- The study was too small to perform a subset analysis of any specific group of patients. Repeating this trial using a more defined group of high-risk surgical patients might demonstrate a significant benefit in the primary endpoint.

Reversal of neuromuscular block by sugammadex

Reversal of profound neuromuscular block by sugammadex administered three minutes after rocuronium: a comparison with spontaneous recovery from succinylcholine.

AUTHORS: Lee C, Jahr JS, Candiotti KA et al.

REFERENCE: *Anesthesiology* (2009) **110**, 1020–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Sugammadex offers a new, efficacious, and safe pharmacological development in anaesthetic practice that permits rapid reversal of neuromuscular blockade instituted with rocuronium, if required.

Impact

The introduction of sugammadex as a safe method to reverse high-dose rocuronium (1.2mg/kg) within minutes of its administration offers a true alternative for anaesthetic practice.

Aims

Succinylcholine (a depolarizing neuromuscular-blocking agent, NMBA) had been the mainstay for the facilitation of tracheal intubation in emergency situations where rapid security of the airway was a priority. Succinylcholine has a variety of adverse problems and contraindications, but no safe alternative had been available. High-dose rocuronium (a non-depolarizing NMBA) can provide equivalent conditions for rapid intubation but has a long duration of action, which is undesirable if difficulties are encountered with airway management. This study aimed to review the efficacy and safety of sugammadex (16mg/kg), given 3min after rocuronium (1.2mg/kg), for reversal of profound neuromuscular block, in comparison with spontaneous recovery from succinylcholine (1mg/kg).

Methods

Patients: 115 patients from 11 institutions in North America.

Inclusion criteria: Adult patients, ASA (American Society of Anesthesiologists) I or II, BMI <30kg/m², scheduled for elective surgery under general anaesthesia.

Exclusion criteria: Relevant CV, respiratory, or neuromuscular comorbidities, (family) history of malignant hyperthermia, or potential contraindications to either of the anaesthetic agents.

Primary endpoints: Time from administration of rocuronium or succinylcholine until recovery of T1 to 10% of its baseline value (measure of strength of response to percutaneous electrical neuromuscular stimulation of the ulnar nerve), and subsequently to 90% of baseline.

Secondary endpoints: Additional efficacy variables recorded, based on neuromuscular monitoring, including recurrence of neuromuscular block in the rocuronium–sugammadex group. Safety assessment made by recording observed/patient-reported adverse events.

Groups: Rocuronium–sugammadex ($n = 55$) or succinylcholine ($n = 55$).

Results

- Mean (SD) time to recovery of T1 to 10%, and subsequently 90%, of baseline values was significantly faster with rocuronium–sugammadex (see Table 20.9);
- Times inclusive of 3min delay before sugammadex administered in that group. Adverse events did not differ significantly, and there was no apparent interaction of sugammadex with other drugs.

Table 20.9 Summary of results

| Time (min) from start of NMBA to recovery of T1 to 10% and 90% | Treatment group | |
|--|------------------------------------|------------------------------|
| | Rocuronium–sugammadex ($n = 55$) | Succinylcholine ($n = 55$) |
| Recovery to T1–10% | | |
| Mean (SD) | 4.4 (0.7) | 7.1 (1.6) |
| Median | 4.2 | 7.1 |
| Min–max | 3.5–7.7 | 3.8–10.5 |
| Recovery to T1–90% | | |
| Mean (SD) | 6.2 (1.8) | 10.9 (2.4) |
| Median | 5.7 | 10.7 |
| Min–max | 4.2–13.6 | 5.0–16.2 |

Sugammadex administered 3min after start of rocuronium administration (mean [SD] 3.1 [0.2]; range 2.7–4.2min).

Discussion

Rocuronium–sugammadex combination offers a real alternative to succinylcholine, when rapid-onset neuromuscular blockade with the option of rapid, safe restoration of neuromuscular function is required (e.g. problems with airway management). The lack of additional complications is promising, and this technique could be used outside the operating theatre, with equal benefits to safety.

Problems

Only compares specific dose regimens, and with a single point at which sugammadex was administered in the rocuronium group. Clinical practice differs according to local guidelines, and this should be considered before extrapolating the findings to wider practice.

Enhanced recovery following major abdominal surgery

Enhanced recovery pathways optimize health outcomes and resource utilisation: a meta-analysis of randomized controlled trials in colorectal surgery.

AUTHORS: Adamina M, Kehlet H, Tomlinson G et al.

REFERENCE: *Surgery* (2011) **149**, 830–40.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Adherence to enhanced recovery pathways (ERPs) achieves a reproducible improvement in the quality of care by enabling standardization of health-care processes. While accelerating recovery and safely reducing hospital stay, ERPs optimize the utilization of resources.

Impact

ERPs can, and should be, routinely used in care after colorectal and other major GI procedures. Anaesthetists need to integrate and help coordinate aspects of the ERP within their planned care for relevant patients.

Aims

ERPs have been proposed as a means to reduce morbidity and improve effectiveness of care. This study aimed to review the evidence supporting the implementation of ERP in clinical practice.

Methods

Patients: 452 patients from six RCTs.

Inclusion criteria: RCTs comparing ERP with traditional care from Medline, Embase, and the Cochrane Library.

Outcome measures: Length of stay; 30d morbidity; readmission rate.

Results

- For patients adhering to ERP, the length of stay decreased by 2.5d (95% credible interval [CrI] −3.92 to −1.11), whereas 30d morbidity was halved (RR 0.52; 95% CrI 0.36–0.73), and readmission was not increased (RR 0.59; 95% CrI 0.14–1.43), compared with patients undergoing traditional care;
- RCTs comparing ERPs to traditional care (TC) (see Table 20.10).

Discussion

The routine use of ERP is a logical step in optimizing the quality and effectiveness of health care. RCTs and prospective studies have demonstrated that ERP markedly improves health outcomes and patient satisfaction. This meta-analysis demonstrates ERPs to reduce 30d morbidity by 52%, and the duration of stay by 2.5d, with no increase in readmission rates.

Table 20.10 Summary of results

| | Length of stay (d) | | Readmission rate; total hospital stay (d) | | Morbidity | |
|--|-----------------------|---------------------------------|---|---------------------|-----------|-------------|
| | ERP | Traditional | ERP | Traditional | ERP | Traditional |
| Anderson UK 2003 11 TC/14 ERP | 3 median 3.96 mean | 7 median* 6.99 mean* | 0% | 0% | 28.6% | 45.5% |
| Delaney et al. USA 2003 33 TC/31 ERP | 5.2 mean | 5.8 mean | 9.7% 5.4 mean | 18.2% 7.1 mean** | 22% | 30% |
| Gatt et al. UK 2005 20 TC/19 ERP | 5 median 6.6 mean | 7.5 median*** 9 mean | 5.3% N/A | 20% N/A | 47.4% | 75% |
| Khoo et al. UK 2007 35 TC/35 ERP | 5 median 5 mean | 7.5 median**** 9 mean | 9% 5 median | 3% 7 median**** | 25.7% | 51.4% |
| Serclova et al. CZ 2009 52 TC/51 ERP | 7 median 7.4 mean | 9 median**** 10.4 mean**** | 0% | 0% | 21.6% | 48.1%**** |
| Muller et al. CH 2009 75 TC/76 ERP | 5 median 6.7 mean | 9 median***** 10.3 mean***** | 3.9% N/A | 3.9% N/A | 21.1% | 49.3%**** |

NB. CH, Switzerland; CZ, Czech Republic; UK, United Kingdom; USA, United States of America. Differences not statistically significant, unless indicated: * $p = 0.002$; ** $p = 0.02$; *** $p = 0.027$; **** $p = 0.001$; ***** $p = 0.003$; ***** $p = 0.0001$.

Problems

- The data supports the incremental benefits of laparoscopic procedures within an ERP. However, larger RCTs are required to define the potential synergies of a laparoscopic approach to an ERP.
- Although technically robust, the study retrieved 389 abstracts, of which 375 did not meet the inclusion criteria. Of the remaining 14 studies, six were excluded for absence of true randomization, and five were discussed separately because they compared a laparoscopic vs an open approach within an ERP. Much evidence was deemed ineligible, and there may have been merit in reviewing some of this further.

Post-operative nausea and vomiting

IMPACT (International Multicentre Protocol to Assess the single and Combined benefits of anti-emetic medication in a controlled clinical Trial): A factorial trial of six interventions for the prevention of postoperative nausea and vomiting.

AUTHORS: Apfel C, Korttila K, Abdalla M *et al.* (IMPACT investigators).

REFERENCE: *N Engl J Med* (2004) 350, 2441–51.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Several treatment strategies reduce the relative risk of post-operative nausea and vomiting (PONV). Prophylaxis for low-risk patients is not deemed cost-effective; however, moderate-risk patients may benefit from a single intervention, and high-risk patients may need multiple interventions.

Impact

Patients should be risk-stratified, in order to tailor treatment.

Aims

PONV is a common complication, often 2° to anaesthetic use. Aside from being unpleasant for patients, vomiting increases the risks of aspiration and other complications, subsequently delaying discharge and increasing costs of patient care. This 26 factorial study aimed to compare adverse outcomes in high-risk patients in whom epidural anaesthesia or an alternative was used for post-operative analgesia.

Methods

Patients: 5,199 patients at 28 international centres.

Inclusion criteria:

- Elective surgery lasting ≥ 1 h;
- $\geq 40\%$ risk of PONV (presence of ≥ 2 risk factors: ♀, non-smoker, previous PONV, motion sickness, anticipated post-operative opioid use).

Exclusion criteria:

- Study drug contraindicated;
- Emetogenic/antiemetic use in previous 24h;
- Expected to require post-operative ventilation;
- Pregnant or lactating.

Groups:

- Antiemetic drug (vs no treatment):
 - Ondansetron ($n = 5,161$);
 - Droperidol ($n = 5,161$);
- Maintenance with propofol (vs inhalational anaesthetic, $n = 5,161$);
- Nitrogen as carrier gas (vs nitrous oxide, N_2O , $n = 4,277$);
- Remifentanyl (vs fentanyl, $n = 4,789$).

Primary endpoint: Incidence of any nausea, emetic episodes (retching or vomiting), or both during first 24 post-operative hours.

Results

Table 20.11 Summary of results

| Intervention | Received intervention | | % RR (95% CI) | <i>p</i> |
|-------------------------------|------------------------|----------------------|---------------------------|----------|
| | YES | NO | | |
| Ondansetron | 735/2,576 (28.5%) | 996/2,585 (38.5%) | -26 (-31.5 to -19.9) | <0.001 |
| Dexamethasone | 739/2,596 (28.5%) | 992/2,565 (38.7%) | -26.4 (-31.9 to -20.4) | <0.001 |
| Droperidol | 742/2,573 (28.8%) | 989/2,588 (38.2%) | -24.5 (-30.2 to -18.4) | <0.001 |
| Propofol* | 1,066/3,427 (31.1%) | 665/1,734 (38.4%) | -18.9 (-25 to -12.3) | <0.001 |
| Nitrogen carrier [†] | 668/2,146 (31.1%) | 755/2,131 (35.4%) | -12 (-19.3 to -4.3) | 0.003 |
| Remifentanyl [‡] | 827/2,386 (34.7%) | 792/2,403 (33%) | 5.2 (-2.9 to 13.8) | 0.2 |

* vs inhalational anaesthetic; [†] vs N₂O as carrier gas; [‡] vs fentanyl.

Discussion

This was the biggest study of prophylaxis for PONV. All of the antiemetic drugs were equally effective. Relative risk reduction was approximately equal to that seen when using total IV anaesthesia (i.e. a combination of substituting a volatile inhalational anaesthetic with propofol for maintenance, and substituting N₂O with nitrogen as a carrier gas). While a maximum relative reduction in risk of PONV of 70% can be achieved by combination of options, this must be offset against the costs and risks of adverse events. (See Table 20.11.)

Problems

- Application of the results to a general surgical population relies upon patients being stratified into being at high risk of PONV. The risk factors for PONV can be ranked as: high-dose opioid use**, history of PONV**, history of motion sickness, non-smokers**, ♀ patients**, type of surgery (high risk associated with gynaecological surgery; middle ear surgery; GI distension; passage of blood into the stomach following ear, nose, and throat, or dental surgery; thyroid and sinus surgery; laparoscopic surgery), early ambulation, and anaesthetic drugs—induction of anaesthesia with etomidate or ketamine, use of N₂O, volatile agents (especially if used for induction of anaesthesia).

** Main factors.

Breast surgery

Introduction 560

Breast cancer screening: benefit vs harm 562

Breast cancer prevention: tamoxifen 564

Breast cancer prevention: anastrozole 566

Breast cancer: breast-conserving surgery vs mastectomy 568

Breast cancer: axillary surgery 570

Breast cancer: oncological safety of immediate breast reconstruction 572

Breast cancer: radiotherapy and breast conserving surgery 574

Radiotherapy for *in situ* breast cancer 576

Polychemotherapy in breast cancer 578

Breast cancer: timing of chemotherapy 580

Tamoxifen for early breast cancer 582

Endocrine therapy for early breast cancer 584

Herceptin for early breast cancer 586

Breast cancer: bisphosphonates for bone metastasis 588

Introduction

Surgery for breast cancer has been performed for over two millennia, with Galen (120–200 AD) being the first to appreciate the importance of clear margins. The treatment of breast cancer stalled in the Dark Ages, with the Council of Tours in 1162 denouncing breast surgery. In 251 AD, Agatha, a young, beautiful virgin, was martyred and became the Patron Saint of the Breast. After rejecting the advances of a powerful Roman magistrate Quintianus, he ordered her breasts amputated, and she died from her wounds. In 1894, Halsted described the en bloc removal of the whole breast, regional lymph nodes, and pectoral muscles. He reported a 40% 5y survival rate, demonstrating markedly improved outcomes, compared to previously published data. In the early 1930s, DH Patey of the Middlesex Hospital in London described the less extensive simple mastectomy, sparing the pectoral muscles.

In Scandinavia, multidisciplinary working emerged in the early 1970s, leading to the development of the concept of breast screening and a more collaborative approach towards patient management. Subsequently, in 1985, Professor Forrest recommended breast screening to be established nationally in the UK, a policy later adopted by Mrs Thatcher's government.

Breast cancer trials started in the 1930s and have made major contributions to the field of EBM. The first major trials involved the use of radiotherapy after mastectomy and were carried out in the UK; those were followed by tamoxifen treatment trials, which have majorly impacted on the management of breast cancer. In the USA, The National Surgical and Adjuvant Breast Project (NSABP), established in 1957, has been responsible for many pivotal breast cancer trials in breast cancer surgery, radiotherapy, chemotherapy, and hormone therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) started in 1985, with the aim of sharing data from high-quality randomized trials worldwide to promote high-quality meta-analyses.

Increasingly, breast cancer is being recognized not as one single pathology, but as a disease with a biology and behaviour that is individual to each patient. This is an exciting time for breast cancer research, which is leading the way in personalized therapies for cancer patients.

Breast cancer screening: benefit vs harm

The benefits and harms of breast cancer screening: an independent review.

AUTHORS: Independent UK Panel on Breast Cancer Screening.

REFERENCE: *Lancet* (2012) **380**, 1778–86.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

In this meta-analysis of 11 RCTs, the RR of breast cancer mortality for women invited to screening, compared with controls, was 0.80 (95% CI 0.73–0.89)—an RRR of 20%. Although the review was based on historical trials and therefore has limited applicability to modern breast cancer management, it was concluded that screening reduces breast cancer mortality, but at the cost of some overdiagnosis (breast cancers diagnosed that would never have caused mortality, if untreated). For every 10,000 UK women aged 50y invited to screening for the next 20y, 43 deaths from breast cancer would be prevented, and 129 cases of breast cancer, invasive and non-invasive, would be overdiagnosed.

Impact

This review provided further evidence to support the continuation of breast screening. However, it is recognized that information should be made available in a transparent and objective way to women invited to screening, so that they can make informed decisions.

Aims

To perform an independent review of the evidence of the benefits and harms of breast screening. This review focused on the impact of screening on mortality and overdiagnosis in the context of the UK breast screening programmes, which currently invite women aged 50–70y for a screening mammography every 3y (to be extended to 47–73y).

Methods

Methods: Reviewed published literature and testimonies from experts in the specialty. RCTs ($n = 10$) used to derive quantitative estimates of benefit.

- Studies included those in Table 21.1.

Results

- **RRR from screening:** Overall RRR, comparing invited vs control women = 0.80 (95% CI 0.73–0.89). Thus, the RRR in breast cancer mortality in the groups invited to screening is estimated to be 20% (95% CI 11–27);
- **ARR from screening:** To determine the absolute benefit of screening in a UK population (i.e. applying the above 20% RRR to the age group screened in the UK), it was estimated that, for every 235 women invited to screening, one breast cancer death would be prevented, representing

Table 21.1 Studies

| Trial | Start date | Number of women | Screening interval (mo) |
|----------------------|------------|-----------------|-------------------------|
| New York HIP | 1963 | 62,000 | 12 |
| Malmö I and II | 1976 | 600,076 | 18–24 |
| Swedish Two Counties | 1977 | 133,065 | 24–33 |
| Canada I and II | 1980 | 89,835 | 12 |
| Stockholm | 1981 | 60,800 | 24–28 |
| Göteborg | 1982 | 52,222 | 18 |
| UK Age trial | 1991 | 160,921 | 12 |

43 breast cancer deaths prevented per 10,000 women invited to screening. For women actually attending breast screening, the absolute benefit is higher, with one breast cancer death prevented for every 180 women screened;

- **Overdiagnosis:** This is the detection of cancers that would never have presented clinically or lead to mortality, if the screening test had not been performed. From the three trials with appropriate F/U data to estimate this, it was determined that there would be an 11% incidence of overdiagnosis in a population invited to screening. Alternatively, this equates to 19% of breast cancers diagnosed through breast screening representing overdiagnosis, or 129 per 10,000 women invited to screening.

Discussion

This review and meta-analysis highlight the uncertainties surrounding the benefits and harm of breast screening. Meta-analyses of these trials are complicated by the heterogeneous methods used such as different age ranges of women screened, screening intervals, and length of F/U.

This review provides independent evidence of a 20% relative reduction in death from breast cancer in women invited for breast cancer screening, a finding consistent with other meta-analyses. However, it highlights a higher rate of overdiagnosis than has hitherto been communicated to women.

Problems

- This review depended on RCTs performed 20–50y ago and observational studies with potential biases.
- Mortality from breast cancer is decreasing—in the UK, European age-standardized mortality rates have dropped from 40.1 per 100,000 in 1990 to 24.4 per 100,000 in 2010. This reduction is largely due to adjuvant treatments such as RT, endocrine therapy, chemotherapy, and trastuzumab. The potential for screening to affect mortality is therefore reducing.

Breast cancer prevention: tamoxifen

P-1 Study: Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.

AUTHORS: Fisher B, Costantino J, Wickerham D *et al.*

REFERENCE: *J Natl Cancer Inst* (1998) **90**, 1371–88.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In women at increased risk of developing breast cancer, tamoxifen, a selective oestrogen receptor modulator (SERM), decreases the incidence of invasive and non-invasive breast cancer.

Impact

Tamoxifen is approved by the US FDA for reducing breast cancer risk. The UK's NICE guidelines (2013) recommend offering tamoxifen for up to 5y to women at high risk of breast cancer, unless they have a past history of thromboembolic disease or endometrial cancer. Despite this, chemoprevention is still infrequently used.

Aims

Contralateral breast cancer incidence decreases, following administration of tamoxifen for adjuvant breast cancer therapy. This RCT, commenced in 1992, aimed to determine whether administration of tamoxifen as 'chemoprevention' could reduce the risk of invasive breast cancer in women at increased risk of breast cancer, with no previous diagnosis of cancer. In addition, because tamoxifen alters lipoprotein metabolism and appears to have a beneficial effect on osteoporosis, the incidence of MIs and bone fractures was determined, as well as safety measures such as VTE and endometrial cancer.

Methods

Patients: 13,175 women at 131 centres in the USA and Canada.

Inclusion criteria:

- Age 60y or older; or
- Age 35–59 with a 5y predicted risk for breast cancer of $\geq 1.66\%$ (using Gail model); or
- History of lobular carcinoma *in situ*;
- No clinical evidence/radiological evidence of breast cancer.

Exclusion criteria:

- History of VTE;
- Hormone replacement therapy (HRT) or oral contraceptive pill within 3mo.

Groups:

- Placebo ($n = 6,707$);
- Tamoxifen ($n = 6,681$).

Primary endpoint: Incidence of invasive and non-invasive breast cancer.

Secondary endpoint: Incidence of endometrial cancer, MI, fractures, PE, and DVT.

Results

Table 21.2 Summary of results

| | Tamoxifen (n = 6,707) | Placebo (n = 6,681) | RR (95% CI) |
|--|--------------------------|------------------------|------------------|
| Discontinued treatment | 1,590 (23.7%) | 1,316 (19.7%) | |
| Invasive breast cancer | 89 | 175 | 0.51 (0.39–0.66) |
| Non-invasive breast cancer | 35 | 69 | 0.50 (0.33–0.77) |
| Annual rate of ER +ve breast cancer/1,000 women | 1.58 | 5.02 | 0.31 (0.22–0.45) |
| Annual rate of ER –ve breast cancer/1,000 women | 1.46 | 1.20 | 1.22 (0.74–2.03) |
| Endometrial cancer | 36 | 15 | 2.53 (1.35–4.97) |
| MI | 31 | 28 | 1.11 (0.65–1.92) |
| Osteoporotic fracture events | 111 | 137 | 0.81 (0.63–1.05) |
| PE | 18 | 6 | 3.01 (1.15–9.27) |
| DVT | 35 | 22 | 1.6 (0.91–2.86) |

ER, oestrogen receptor.

- The reduction in invasive breast cancer in the tamoxifen arm was similar across all age groups (≤ 49 , 50–59, ≥ 60);
- The proportion of women reporting bothersome hot flushes was 45.7% in the tamoxifen group, compared with 28.7% with placebo. (See Table 21.2.)

Discussion

This trial reported a 49% reduction in invasive breast cancer, and a 50% reduction in non-invasive breast cancer, in women taking tamoxifen chemoprevention. In 2005, 7y F/U data were reported. Despite the potential bias caused by unblinding, similar event rates for breast cancer and secondary endpoints were reported. Indeed, almost one-third of placebo participants commenced chemoprevention, following unblinding. Despite the increase in endometrial cancer and VTE in the tamoxifen arm, the authors concluded that tamoxifen chemoprevention is appropriate in many women at increased risk of breast cancer. Longer F/U did not demonstrate a reduction in ischaemic heart disease with tamoxifen. IBIS-I (*Lancet* 2002) reported similar findings to the P-1 Study, with a 32% risk reduction in breast cancer, but a significant increase in thromboembolic events with tamoxifen.

Problems

- Only 3.6% of patients were non-white, limiting the applicability to other ethnic groups.
- Over one-fifth of patients discontinued therapy. Individual compliance to therapy was not reported.
- Study unblinded prior to survival benefit being demonstrated; however, the marked reduction in breast cancer incidence dictated the unblinding.
- Longer F/U required to determine the full benefit of chemoprevention.

Breast cancer prevention: anastrozole

IBIS-II: Anastrozole for prevention of breast cancer in high-risk post-menopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial.

AUTHORS: Cuzick J, Sestak I, Forbes J *et al.* (IBIS-II Investigators)

REFERENCE: *Lancet* (2014) **383**, 1041–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Oestrogen is a key factor in the development of breast cancer. Extra-ovarian oestrogen production (the 1° source of oestrogen in post-menopausal women) can be inhibited by aromatase inhibitors (AIs). AIs, in the adjuvant setting, have increased efficacy for the prevention of breast cancer recurrence and contralateral cancer, compared to tamoxifen. This study demonstrated that anastrozole, an AI, reduced breast cancer incidence in high-risk post-menopausal women, with limited evidence supporting good tolerability of anastrozole.

Impact

This study provides evidence that, in the post-menopausal setting, chemoprevention for breast cancer is safe and has an acceptable SE profile for women at high risk of breast cancer.

Aims

A meta-analysis of RCTs on SERMS, e.g. tamoxifen, for chemoprevention demonstrated a 51% reduction in ER-positive breast cancers. This double-blind RCT sought to determine whether this reduction extended to the AI anastrozole (1mg od for 5y) and determine the safety of anastrozole in the prevention setting.

Methods

Patients: 3,864 women, from 153 centres in 18 countries.

Inclusion criteria:

- Post-menopausal women, aged 40–70;
- Increased risk of breast cancer (age 40–44 RR $\times 4$; age 45–59 RR $\times 2$; age 60–70 RR $\times 1.5$).

Exclusion criteria:

- Premenopausal status;
- Previous breast cancer;
- Intention to continue HRT;
- Severe osteoporosis.

Groups:

- Placebo ($n = 1,944$);
- Anastrozole ($n = 1,920$): 1mg od for 5y.

Primary endpoint : Invasive and non-invasive breast cancer.

Secondary endpoint:

- ER-positive breast cancer;
- Mortality (breast cancer and other);
- Fractures and adverse events.

Results**Table 21.3** Summary of results

| | Anastrozole (n = 1,920) | Placebo (n = 1,944) | HR (95% CI) | p |
|------------------------------|----------------------------|------------------------|------------------|---------|
| Discontinued treatment | 469 (24%) | 396 (20%) | | |
| Invasive breast cancer | 32 (2%) | 64 (3%) | 0.50 (0.32–0.76) | 0.001 |
| Non-invasive breast cancer | 6 (<1%) | 20 (1%) | 0.30 (0.12–0.74) | 0.009 |
| ER +ve breast cancer | 20 (1%) | 47 (2%) | 0.42 (0.25–0.71) | 0.001 |
| ER –ve breast cancer | 11 (1%) | 14 (1%) | 0.78 (0.35–1.72) | 0.538 |
| Breast cancer mortality | 2 (<1%) | 0 | | |
| Other mortality | 16 (<1%) | 17 (<1%) | | 0.8 |
| Other cancer | 40 (2%) | 70 (4%) | 0.58 (0.39–0.85) | 0.005 |
| Osteoporotic fracture events | 164 (9%) | 149 (8%) | 1.11 (0.90–1.38) | |
| Vasomotor effects | 1,090 (57%) | 961 (49%) | 1.15 (1.08–1.22) | <0.0001 |
| Musculoskeletal | 1,226 (64%) | 1,124 (58%) | 1.10 (1.05–1.16) | 0.0001 |

Discussion

IBIS-II reported its findings at a median 5y F/U. The authors estimated 36 women (95% CI 33–44) would need to be treated with anastrozole to prevent one cancer in 7y of F/U. The reduction in breast cancer with anastrozole is greater than reported for SERMs. No benefit recorded for ER-negative breast cancer. Anastrozole appeared more effective in reducing the rate of high-grade than low-grade tumours. (See Table 21.3.)

Fracture rates was similar in both arms; however, one-sixth were taking bisphosphonates (330 [17%] in the anastrozole group vs 297 [15%] in the placebo group). Venous thrombosis was 1% in both groups. Vasomotor and musculoskeletal symptoms were common in both groups, though significantly commoner with anastrozole. The clinical significance of this difference is unclear.

Problems

- No validated questionnaires used for QoL or SEs.
- Compliance data are not clearly reported, which would have provided a clinically relevant measure of the impact of the reported SEs.
- Further F/U is required to see if the effect persists for >10y (as has been shown with tamoxifen).
- The reduction in other cancers (particularly colorectal and non-melanoma skin cancer) is unexpected and requires further investigation.

Breast cancer: breast-conserving surgery vs mastectomy

Twenty-year follow-up of a randomized controlled trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer.

AUTHORS: Fisher B, Anderson S, Bryant J *et al.*

REFERENCE: *N Engl J Med* (2002) **347**, 1233–41 (updated to *N Engl J Med* (1989) **320**, 822–8).

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Breast-conserving surgery (BCS) (lumpectomy or local excision), combined with RT, is equal to mastectomy, in terms of local control and overall survival.

Impact

Following this study, BCS, followed by RT, has become widely accepted as the treatment of choice for most women with small (<4cm) breast cancers that are unifocal. The omission of RT after BCS is considered substandard.

Aims

The initial results (published in 1985 by the same group) and subsequent 8y F/U data reported that women undergoing lumpectomy and irradiation had comparable local control and overall survival. This latest report aimed to provide longer-term (20y F/U) data in the assessment of whether BCS, followed by RT, provided equivalent local and distant disease control to mastectomy.

Methods

Patients: 1,851 patients from multiple centres across the USA.

Inclusion criteria:

- Stage I or II breast cancer (tumour size <4cm);
- Margins of receptor specimen free of tumour;
- No metastasis.

Exclusion criteria:

- Women in whom the margin was involved after BCS subsequently underwent mastectomy and were excluded from the results of the BCS group;
- Patients not suitable for RT.

Groups:

- BCS ($n = 634$);
- BCS and RT ($n = 628$);
- Mastectomy ($n = 589$).

Primary endpoint: Local recurrence.

Secondary endpoints:

- Distant disease-free survival (DFS);
- Overall survival.

Results**Table 21.4** Summary of results

| Event | Mastectomy (n = 589) | BCS (n = 634) | BCS and RT (n = 628) |
|--------------------------|-------------------------|------------------|-------------------------|
| Recurrence | 219 (37.2) | 269 (42.4) | 214 (34.1) |
| Local | 60 (10.2) | 56 (8.8) | 17 (2.7) |
| Distant (mets) | 132 (22.4) | 158 (24.9) | 163 (26.0) |
| Second cancer | 43 (7.3) | 32 (5.0) | 49 (7.8) |
| Death from another cause | 59 (10.0) | 51 (8.0) | 69 (11.0) |
| Alive | 218 (37.0) | 226 (35.6) | 237 (37.7) |

BCS, breast-conserving surgery; RT, radiotherapy.

- Equivalent local and distant recurrence was achieved with BCS, compared with mastectomy, for patients with stages I/II breast cancer;
- Local control was significantly better for patients undergoing BCS + RT vs BCS alone. Overall survival did not differ ($p = 0.23$, ns);
- Local recurrence rate in patients receiving no RT was significantly worse than those receiving BCS and RT ($p < 0.001$). (See Table 21.4.)

Discussion

This trial confirmed the efficacy of wide local excision with irradiation and ushered in an era of BCS for the treatment of stages I/II breast cancer. The long-term data continue to support this conclusion. Subsequently, other trials comparing wide local excision and RT vs mastectomy have shown no difference, and a meta-analysis of the two treatments has shown equal recurrence rates and survival in both groups at 5y.

Problems

- The trial ensured mastectomy for all patients whose initial conservative surgery did not clear margins, whereas today most people undergo re-excision.
- The inclusion of patients who had margins involved in the mastectomy group may have biased the recurrence rate in this arm.

Breast cancer: axillary surgery

A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer.

AUTHORS: Veronesi U, Paganelli G, Viale G *et al.*

REFERENCE: *N Engl J Med* (2003) **349**, 546–53.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Seventy percent of breast cancer patients are node-negative. Axillary surgery, in the form of axillary dissection, leads to arm swelling, lymphoedema, and loss of sensation. Which patients are node-negative can be predicted by sentinel node biopsy; this can avoid axillary clearance, while preventing morbidity associated with the procedure.

Impact

Sentinel node biopsy is now accepted as the treatment of choice for women with small breast cancers, including screening-detected breast cancers.

Aims

Breast cancer screening allows the diagnosis of cancer to be made at an early stage and at a time when the axillary nodes are likely to be free of disease. Axillary dissection is a procedure that can be associated with considerable morbidity. Furthermore, the cost to the UK's NHS of treatment for complications, such as arm swelling and lymphoedema associated with axillary clearance surgery, is ~ £200 million per year. Therefore, reducing these complications by more conservative sentinel node biopsy is a priority. The aim of this study was to determine the safety and morbidity from sentinel node biopsy when used to stage breast cancer.

Methods

Patients: 516 women at one centre in Italy.

Inclusion criteria:

- Tumour ≤ 2 cm in diameter;
- Clinically node-negative.

Exclusion criteria:

- Previous invasive breast cancer;
- Previous treatment for invasive breast cancer;
- Clinically node-positive cancers;

Groups:

- Sentinel node biopsy ($n = 259$);
- Axillary clearance ($n = 257$).

Primary endpoint: Predictive power of the status of sentinel node, measured in terms of the % cases of axillary involvement detected by sentinel node biopsy in relation to the % found by axillary dissection.

Secondary endpoints:

- Indicators of QoL;
- Number of axillary node metastasis appearing during F/U;
- DFS and overall survival.

Results

Table 21.5 Summary of results

| | Sentinel node biopsy (<i>n</i> = 259) | Axillary clearance (<i>n</i> = 257) | <i>p</i> |
|-------------------------|---|---|----------|
| Positive sentinel node | <i>n</i> = 92 (35.5%) (95% CI 29.7–41.7) | <i>n</i> = 83 (32.3%) (95% CI 26.6–38.4) | ns |
| Axillary pain (at 24mo) | 8% | 39% | <0.001 |
| Arm swelling (at 24mo) | 1% | 37% | <0.001 |
| Recurrence | <i>n</i> = 13 | <i>n</i> = 21 | ns |
| Deaths | <i>n</i> = 1 | <i>n</i> = 2 | ns |

Discussion

This, and the subsequent ALMANAC trial (*J Natl Cancer Inst* (2006) **98**, 599–609), demonstrated that sentinel node biopsy was an appropriate method for staging the axilla. Sentinel node biopsy was carried out using a radioisotope and a colloid-linked blue dye injected either around the tumour or underneath the ipsilateral areola, allowing tracking of the isotope and dye to the first (sentinel) node in the axilla. This was removed at axillary surgery, and, where it was clear, no further axillary dissection was required. For those patients in whom nodes were involved, further dissection of the axilla was required. (See Table 21.5.)

Problems

- F/U was short, and therefore the risk of axillary recurrence was unclear (although it did appear to be low).
- Study morbidity was only examined in detail in 200 of the total number of patients recruited (100 in each group) but was clearly lower in the sentinel node biopsy group.
- It is unclear whether optimal treatment for patients who are sentinel node-positive is axillary clearance, RT to the axilla, or even no further treatment. This is the basis of further trials ongoing in both the USA and Europe.

Breast cancer: oncological safety of immediate breast reconstruction

Immediate reconstruction with implants in women with invasive breast cancer does not affect oncological safety in a matched cohort study.

AUTHORS: Eriksen C, Frisell J, Wickman M *et al.*

REFERENCE: *Breast Cancer Res Treat* (2011) 127, 439–46.

STUDY DESIGN: Retrospective case control.

EVIDENCE LEVEL: 3.

Key message

Over 60% of breast reconstructions are performed at the time of mastectomy. This allows preservation of a more native (breast) skin, improving long-term cosmetic outcome and avoiding a period of being 'flat'. The 1st aim of immediate breast reconstruction is to improve psychological well-being and health-related QoL. This retrospective study provided the best evidence to date of the oncological safety of immediate breast reconstruction.

Impact

This study supports current guidelines that immediate breast reconstruction should be considered for all women with invasive breast cancer undergoing mastectomy.

Aims

~15,000 women undergo mastectomy in the UK per annum, with 20% having immediate breast reconstruction. However, there are concerns about the oncological safety of immediate breast reconstruction: (a) resection of breast tissue could be compromised with a skin-sparing technique; (b) adjuvant therapy may be delayed, because of wound problems; (c) RT may be compromised by the presence of implant or concerns about a negative cosmetic outcome; and (d) reconstruction could lead to a delay in the presentation of local recurrence. In this study, patients who had undergone immediate breast reconstruction were matched (using a cancer registry) to non-reconstructed breast cancer mastectomy patients, in order to evaluate long-term outcomes.

Methods

Patients: 300 women having immediate breast reconstruction, from the Karolinska University Hospital, matched to 300 women from the regional (Stockholm-Gotland) breast cancer registry.

Inclusion criteria: Cases:

- Invasive breast cancer;
- Implant-based reconstruction (IBR).

Controls (mastectomy only) matched by four categories:

- Age ($\pm 5y$);
- Tumour size (0–20mm, 21–50mm, and >50mm);
- Nodal status (0, 1–3, ≥ 4);
- Year of operation ($\pm 3y$).

Primary endpoint: Local recurrence.

Secondary endpoints:

- Distant recurrence;
- Time to oncological treatment;
- DFS;
- Breast cancer-specific survival.

Results**Table 21.6** Summary of results

| Total number of events (%) | IBR (n = 300) | Controls (n = 300) | HR (95% CI) | p |
|---|------------------|--------------------|---------------|------|
| Overall recurrence | 28.45% | 32.85% | 1.2 (0.9–1.7) | 0.3 |
| Local recurrence | 8.2% | 9.0% | 1.0 (0.5–1.8) | 1.0 |
| Distant metastases | 20.3% | 27.1% | 1.4 (1.0–2.1) | 0.07 |
| Death, all causes | 22.0% | 28.0% | 1.5 (1.0–2.1) | 0.04 |
| Death, breast cancer | 17.0% | 23.0% | 1.6 (1.1–2.4) | 0.03 |
| Time to chemotherapy (median [range], wk) (n) | 5.0 (2–22) (112) | 5.1 (2–33) (105) | | 0.4 |
| Time to radiotherapy (median [range], wk) (n) | 24.1 (6–48) (86) | 24.7 (5–42) (70) | | 0.9 |
| Complications <30d | 7.3% | 6.3% | | 0.6 |

Discussion

This study provided reassuring long-term (11+ years) evidence that immediate breast reconstruction was safe. However, there are limitations to such a retrospective study, detailed below. In general, the quality of evidence for oncoplastic surgery is low. Randomized trials (e.g. QUEST) have struggled to recruit, with patients and surgeons reluctant to leave the operative choice to randomization. More thorough ongoing prospective cohort data collection, including patient-reported outcome measures (PROMs), are required. (See Table 21.6.)

Problems

- Patients with inflammatory breast cancer, locally advanced disease, and high BMI, and heavy smokers were not offered immediate reconstruction, limiting the applicability of this study. Similarly, groups were not matched for performance status, and it is likely that the IBR group would have a higher performance status, explaining the increased all-cause mortality in the control group.
- The majority of patients (>280 per group) had adjuvant chemotherapy and RT; however, time-to-treatment data are markedly incomplete. This study is limited to women undergoing IBR. Patients having autologous flap-based reconstruction undergo more extensive surgery and may be at increased risk of delayed healing, affecting the time to adjuvant therapy.
- Significantly more women in the reconstruction arm were ER-positive (80% vs 69%)—a better prognosis subgroup—which may explain the improved breast cancer-specific mortality in this group.

Breast cancer: radiotherapy and breast conserving surgery

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials.

AUTHORS: Darby S, McGale P, Correa C et al.

REFERENCE: *Lancet* (2011) **378**, 1707–16.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

RT is required after BCS to prevent local recurrence and improve overall survival. Overall, about one breast cancer death was avoided by y 15 for every four recurrences avoided by y 10, in node-negative and node-positive disease.

Impact

RT is now considered standard practice after BCS for invasive disease.

Aims

RT has been considered a necessary adjunct to BCS—an approach that has been demonstrated to confer similar survival rates to mastectomy. However, RT is not without its own risks and complications. For this reason, several RCTs have been conducted to compare outcomes following BCS, with and without RT. This meta-analysis aimed to report long-term F/U data on these RCTs, focusing on 10y local recurrence rates and how they impacted 15y mortality. It also aimed to identify patient groups with high and low absolute benefits from RT.

Methods

Patients: 10,801 women from 17 RCTs.

Inclusion criteria: RCTs of adjuvant RT vs no RT, following BCS for invasive cancer commencing prior to 2000.

Exclusion criteria: Metastatic disease.

Primary endpoint: First recurrence.

Secondary endpoint:

- Breast cancer death;
- All-cause death.

Results

Table 21.7 Summary of results

| | BCS + RT | BCS only | Rate ratio (95% CI) |
|---|----------|----------|---------------------------------------|
| 10y recurrence rate (locoregional or distant) | 19.3% | 35.0% | 0.52 (0.48–0.56); $p < 0.00001$ |
| 15y breast cancer death | 21.4% | 25.2% | RR 0.82 (0.75–0.90); $p = 0.00005$ |
| 15y any death | 34.6% | 37.6 | RR 0.92 (0.86–0.99); $p = 0.03$ |

- The 10y risk of any recurrence (locoregional or distant) corresponds to an ARR with RT of 15.7% (95% CI 13.7–17.7, $p < 0.00001$);
- The 15y ARR in breast cancer death was 3.8% (95% CI 1.6–6.0, $p = 0.00005$), suggesting, on average, about one breast cancer death avoided for every four recurrences avoided by RT. (See Table 21.7.)

Discussion

After BCS, RT halved the average annual rate of any first recurrence and reduced the annual breast cancer death rate by one-sixth. These proportional benefits vary little between different groups of women. By contrast, the absolute benefits from RT vary substantially, according to the characteristics of the patient. For example, older women with low-grade tumours had substantially less absolute benefit from RT. Thus, in selected patients, RT may not add greatly to the value of treatment. However, for the majority of patients treated with BCS, RT should be mandatory, following surgery.

Problems

- It should be noted that RT administration has radically changed since 2000, with the advent of intensity-modulated RT and partial breast RT trials.
- This was a pooled analysis, which may therefore be subject to publication bias or lack of transparency in patient allocation.

Radiotherapy for *in situ* breast cancer

Breast-conserving treatment with or without radiotherapy in ductal carcinoma *In Situ*: 15-year recurrence rates and outcome after a recurrence, from the EORTC 10853 randomized phase III trial.

AUTHORS: Donker M, Litière S, Werutsky G *et al.*

REFERENCE: *J Clin Oncol* (2013) **31**, 4054–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

RT after BCS for ductal carcinoma *in situ* (DCIS) confers benefits over BCS alone in preventing local recurrence. At 15y, almost one in three non-irradiated women developed a local recurrence after BCS for DCIS. RT reduced this risk by a factor of two.

Impact

Although RT reduced local recurrence (both invasive and *in situ*), no effects on overall survival were seen, with deaths from breast cancer similar in both groups due to the failure of RT to prevent metastasis. RT is still used in women at high risk of local recurrence after BCS with DCIS.

Aims

BCS has become an increasingly popular option for patients with DCIS, providing a more satisfactory cosmetic appearance than mastectomy. Studies had demonstrated BCS to be as effective as mastectomy. However, with an increasing incidence of DCIS detection due to breast cancer screening programmes, the risk of residual disease with BCS remained a concern. This study aimed to present long-term F/U data for the original EORTC (European Organisation for Research and Treatment of Cancer) study (*Lancet* (2000) **355**, 528–33) to determine optimal adjuvant RT after local excision of DCIS of the breast.

Methods

Patients: 1,010 women from 46 centres in 13 European countries.

Inclusion criteria: Locally excised DCIS with intent to remove the whole lesion.

Exclusion criteria:

- Incompletely excised DCIS or DCIS >4cm in size;
- Age >70y;

Groups: Allocated after breast-conserving wide local resection surgery:

- RT ($n = 507$);
- No further treatment ($n = 503$).

Primary endpoint: Invasive and non-invasive recurrence in the treated breast.

Secondary endpoints:

- Distant metastases;
- Breast cancer-specific survival.

Results**Table 21.8** Summary of results

| | Number of events | 15y recurrence-free rates | HR (95% CI) | p |
|---------------------------------|------------------|---------------------------|------------------|--------|
| All local recurrence | 149 | 69% | 0.52 (0.40–0.68) | <0.001 |
| BCS | 85 | 82% | | |
| BCS + RT | | | | |
| DCIS recurrence | 74 | 84% | 0.49 (9.33–0.73) | 0.003 |
| BCS | 38 | 92% | | |
| BCS + RT | | | | |
| Invasive recurrence | 75 | 84% | 0.61 (0.42–0.87) | 0.0007 |
| BCS | 48 | 90% | | |
| BCS + RT | | | | |
| Distant metastases | 33 | 93% | 0.99 (0.61–1.61) | 0.982 |
| BCS | 33 | 93% | | |
| BCS + RT | | | | |
| Breast cancer-specific survival | 22 | 95% | 1.07 (0.60–1.91) | 0.814 |
| BCS | 24 | 95% | | |
| BCS + RT | | | | |

Discussion

Treatment with adjuvant RT after BCS approximately halved the risk of local recurrence. The risk of local recurrence was highest during the first 5y of the study (hazard rates of 4.0%/year in the BCS group and 2.0%/year in the BCS + RT group). The risk then decreased to 2.0% and 1.2% in the BCS and BCS + RT groups, respectively, in the next 5y, and to 1.3% and 0.6%, respectively, from 10y onward.

This trial confirmed previous data from the USA that RT prevented local recurrence. However, 30% of patients were subsequently shown to have margin involvement on histopathological review. No effect on overall survival was seen, due to the frequency of distant metastasis being similar in both groups. (See Table 21.8.)

Problems

- Numbers with involved margins limit the strength of the findings.
- The lack of overall effect on survival has left considerable argument as to the value of adjuvant RT.
- The trial confirmed the benefit of using RT after BCS for DCIS, although the magnitude of the benefit and value in preventing local recurrence remains contentious.

Polychemotherapy in breast cancer

Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials.

AUTHORS: Peto R, Davies C, Godwin J et al.; Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

REFERENCE: *Lancet* (2012) **379**, 432–44.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Polychemotherapy reduces breast cancer mortality by approximately one-third. RRR remains consistent for all tumour and patient characteristics, including age, nodal status, tumour size, and oestrogen receptor (ER) status. The actual benefit of chemotherapy depends on an individual's risk of recurrence balanced against co-morbidity and complications induced by chemotherapy.

Impact

This study reports the benefits of chemotherapy over no chemotherapy. It also reports the additional benefit of adding taxanes to anthracycline-based chemotherapy. However, it also finds that the relative benefits of chemotherapy are similar in all patient and tumour subgroups, highlighting the need to consider absolute benefits when considering the further benefit of adjuvant chemotherapy.

Aims

This meta-analysis aimed to review the long-term outcomes of all breast cancer chemotherapy RCTs.

Methods

Patients: Women with breast cancer who had:

- Taxane + anthracycline vs anthracycline alone ($n = 44,000$, 33 trials, begun in 1994–2003);
- Anthracycline vs CMF (cyclophosphamide, MTX, and fluorouracil) ($n = 18,000$, 20 trials, begun in 1978–1997);
- Polychemotherapy vs no adjuvant chemotherapy ($n = 32,000$, 64 trials, begun in 1973–1996):
 - Anthracycline vs no chemotherapy;
 - CMF vs no chemotherapy.

Primary endpoint: Breast cancer mortality.

Secondary endpoints:

- Recurrence rate;
- Other mortality.

Results

Table 21.9 Summary of results

| | Endpoint | Rate ratio (SE) | p |
|---|-------------------------|-----------------|----------|
| Taxane + anthracycline vs anthracycline | Recurrence | 0.70 (0.04) | <0.00001 |
| | Breast cancer mortality | 0.76 (0.05) | <0.00001 |
| | Other mortality | 1.24 (0.12) | 0.05 |
| Anthracycline vs CMF | Recurrence | 0.93 (0.03) | 0.01 |
| | Breast cancer mortality | 0.89 (0.03) | 0.0006 |
| | Other mortality | 1.02 (0.09) | |
| CMF vs no chemotherapy | Recurrence | 0.70 (0.04) | <0.00001 |
| | Breast cancer mortality | 0.76 (0.05) | <0.00001 |
| | Other mortality | 1.24 (0.12) | 0.05 |
| Anthracycline vs no chemotherapy | Recurrence | 0.73 (0.03) | <0.00001 |
| | Breast cancer mortality | 0.79 (0.04) | <0.00001 |
| | Other mortality | 1.2 (0.1) | 0.05 |

Discussion

CMF and anthracycline showed similar benefits, with recurrence rates reduced by one-third and mortality by 20–25%. Higher-dose chemotherapy (including the addition of taxane) appeared more effective, with a potential further proportional reduction of 15–20% in breast cancer mortality rates. The proportional reductions in recurrence and breast cancer mortality appeared largely independent of age, nodal status, tumour diameter, tumour differentiation, or ER status.

These findings highlight the need for more individualized assessment of recurrence risk to allow absolute, rather than relative, benefits of chemotherapy to be determined. Oncotype DX is one tool that is improving our ability to do this and is increasingly available, having recently received NICE approval in the UK. Prospective trials of its clinical utility are awaited. (See Table 21.9.)

Problems

- Relatively few patients were aged >70y.
- Although the ER status was reliable enough to predict response to endocrine therapy, this was not centrally measured. Additionally, modern markers of tumour cell biology, such as quantitative immunohistochemistry (IHC) or ER, progesterone receptor (PR), Her2 and Ki67, were not performed.
- There was marked patient heterogeneity within many of the trials, particularly the older trials.
- Relatively few patients had small, better prognosis cancers in these current trials, compared to the majority of (screening population) breast cancer patients currently being treated.

Breast cancer: timing of chemotherapy

Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis.

AUTHORS: Mauri D, Pavlidis N, Ioannidis J.

REFERENCE: *J Natl Cancer Inst* (2005) **97**, 188–94.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Compared with standard post-operative adjuvant therapy, neoadjuvant chemotherapy showed no improvement in survival. However, where RT was given without surgery, increased locoregional recurrence was seen.

Impact

1° neoadjuvant chemotherapy is now an accepted treatment modality for large 1° cancers.

Aims

Increasing consideration of non-metastatic breast cancer as a systemic (rather than local) disease has led to an interest in the role of neoadjuvant chemotherapy to treat the early systemic signs of the disease. Local chemotherapy response can range from tumour regression to a complete pathological response. This meta-analysis aimed to determine the benefits of preoperative chemotherapy in early breast cancer on local/distant recurrence and overall survival.

Methods

Patients: 3,946 women from nine trials of 1° systemic chemotherapy vs post-operative adjuvant chemotherapy.

Inclusion criteria:

- Large invasive breast cancers unsuitable for BCS;
- Suitable for chemotherapy;
- No prior treatment.

Exclusion criteria:

- Patients unsuitable for chemotherapy;
- Prior surgical treatment;
- Metastatic breast cancer.

Primary endpoint: Overall survival.

Secondary endpoints:

- Locoregional recurrence;
- Distant recurrence;
- Clinical and pathological response rate to chemotherapy.

Results

- Of 3,946 randomized patients (1,972 neoadjuvant arm, 1,074 adjuvant arm), there were 1,310 occurrences of disease progression and 966 deaths;
- No differences in overall survival between 1° systemic therapy and adjuvant therapy;
- In those patients given 1° systemic therapy and in whom surgery was subsequently omitted because of an incomplete response, there was increased locoregional recurrence, despite RT. (See Table 21.10.)

Table 21.10 Summary of results

| | (RR = relative risk) |
|----------------------------|---------------------------|
| Primary measurable outcome | RR 1.00, 95% CI 0.90–1.12 |
| Disease progression | RR 0.99, 95% CI 0.91–1.07 |
| Disease recurrences | RR 0.94, 95% CI 0.83–1.06 |
| Locoregional recurrence | RR 1.22, 95% CI 1.03–1.44 |

Discussion

1° systemic therapy conferred no survival difference, although it did reduce the need for mastectomy. A good prognosis was achieved for those patients who achieved complete tumour remission with chemotherapy. But for those in whom no response was seen, prognosis remained poor. Altogether, one-third of patients had died by the time of this meta-analysis, indicating a generally poor response to treatment, whether given before or after surgery in this group of patients.

Problems

- This meta-analysis of nine trials included significant variation between treatments offered, and subsequently between whether or not surgery and RT or RT alone was given. Nonetheless, the study indicated clearly that neoadjuvant therapy was as safe as systemic therapy, in terms of overall survival.

Tamoxifen for early breast cancer

EBCTG (Early Breast Cancer Trialists' Collaborative Group): Tamoxifen for early breast cancer: an overview of the randomised trials.

AUTHORS: Early Breast Cancer Trialists' Collaborative Group.

REFERENCE: *Lancet* (1998) **351**, 1451–67.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

The use of tamoxifen in ER-positive or unknown 1° breast tumours is associated with a significant reduction in the risk of recurrence and improvement in 10y overall survival. However, there is an increase in incidence of endometrial cancer.

Impact

This is one of a series of 5-yearly systematic reviews started in 1984 by this group. They have provided solid data on which to base breast cancer treatment, revolutionizing practice. Endocrine therapy with agents, such as tamoxifen, is now standard treatment for all patients with ER-positive breast cancer. The benefit of the treatment depends on the level of ER expression, but up to a 40% reduction in recurrence is achieved with treatment for 5y.

Aims

The aims of the studies incorporated into this meta-analysis were to determine the benefit of tamoxifen in women with early breast cancer, after surgical and local treatment had been conducted. Initial trials did not select patients by the presence of ER positivity, but subsequently all trials selected patients by ER type. This updated overview consolidated the information obtained from previous studies on adjuvant tamoxifen use.

Methods

Patients: 36,689 women from 55 RCTs that began before 1990 (87% of worldwide evidence). Data collected/finalized from 1995 to 1996 were analysed.

Inclusion criteria: Patients aged between 18 and 70y, with early breast cancer (restricted to the breast) and no distant disease.

Exclusion criteria:

- Metastatic breast cancer;
- Previous VTE;
- Pregnancy.

Data collected:

- Age and menopausal status;
- Nodal involvement; ER and PR status;
- Treatments (1, 2, or 5y of tamoxifen) and outcomes.

Statistics: Comparisons based on ITT principle. Each trial analysed separately and then combined. Two-sided significance tests used.

Groups: Adjuvant tamoxifen 20mg/d for 1, 2, or 5y.

Primary endpoint: Breast cancer mortality.

Secondary endpoints: Breast cancer recurrence and adverse events.

Follow-up: Median F/U 10y.

Results

Table 21.11 Summary of results

| | Reduction in recurrence (vs placebo) | Reduction in all-cause mortality |
|-----------------|---|-------------------------------------|
| Tamoxifen (1y) | 18%, SD 3 ($p < 0.0001$) | 10%, SD 3 |
| Tamoxifen (2y) | 25%, SD 2 ($p < 0.0001$) | 15%, SD 2 |
| Tamoxifen (3y+) | 42%, SD 3 ($p < 0.01$) | 22%, SD 4 |
| Overall | 26.4%, SD 1.5 ($p < 0.001$) | 14.5%, SD 1.5 |
| ER-poor | 6%, SD 11 | -3%, SD 11 |
| ER-unknown | 37%, SD 8 | 21%, SD 9 |
| ER-rich | 43%, SD 3 ($p < 0.0001$) | 23%, SD 4 ($p < 0.0001$) |

SD, standard deviation.

Discussion

This meta-analysis concluded that 5y tamoxifen provided the optimal standard of care for ER-positive cancers. The greatest benefit was found in those at highest risk (i.e. node-positive tumours). Both pre- and post-menopausal women benefited. Although recurrence reductions occurred early in the first 5y period, mortality reductions commenced after 3y and continued to increase up to 10y. Thus, 5y treatment had a longer impact on recurrence and mortality, even once the drug was stopped. There was an absolute decrease of 50% in contralateral breast cancer, but coincidentally there was a 2.58 times higher incidence of endometrial cancer, with an annual excess of deaths of 0.2 per 1,000. The reduction in contralateral breast cancer was maximal for ER-rich patients, with a 47% reduction (SD 9), whereas, for ER-poor patients, there was a non-significant reduction in contralateral breast cancer. The effects were seen regardless of age at diagnosis. There was no increase in the incidence of colorectal cancer. Tamoxifen should not be used concurrently with chemotherapy, due to an increased risk of VTE. The fourth cycle (presented in 2000) included data from 200,000 women (400 RCTs from 250 groups). This demonstrated the benefits (for 15y survival) of treatment with chemotherapy (e.g. FAC: 5-fluorouracil, adriamycin, cyclophosphamide) and hormonal therapy (e.g. tamoxifen in ER-positive disease). There was also some benefit on mortality from improved local disease control by surgery and RT. (See Table 21.11.)

Endocrine therapy for early breast cancer

ATAC trial: Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial.

AUTHORS: Cuzick J, Sestak I, Baum M; ATAC/LATTE investigators.

REFERENCE: *Lancet Oncol* (2010) **11**, 1135–41.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

ATAC was the first trial to show that an AI was more effective and had fewer serious SEs than tamoxifen in the adjuvant setting. This study provides an update to the findings of ATAC, first reported in 2002 (*Lancet* (2002) **359**, 2131–9). In post-menopausal women with hormone receptor-positive early breast cancer, there is a 2.7% absolute reduction at 5y of breast cancer recurrence and a 4.3% reduction at 10y, compared with tamoxifen.

Impact

AIs are now an integral part of adjuvant therapy for breast cancer.

Aims

Many breast cancers are dependent upon oestrogens for their growth. Adjuvant tamoxifen is an established treatment in those with ER-positive tumours, demonstrated to improve DFS and overall survival. However, long-term survival has been associated with the development of complications, including an increased incidence of endometrial cancer. AIs inhibit the synthesis of oestrogen from androgens in post-menopausal women, with anastrozole reported to be a well-tolerated agent demonstrated to confer a survival advantage. This study aimed to evaluate and compare the effects of anastrozole with tamoxifen, or combination therapy, on disease recurrence and breast cancer mortality in post-menopausal women with hormone receptor-positive early breast cancer.

Methods

Patients: 9,366 women at 381 international centres.

Inclusion criteria:

- Post-menopausal women;
- Early breast cancer;
- ER-positive or unknown;
- Completed 1° surgery and chemotherapy.

Exclusion criteria:

- ER-negative cancer;
- Previous tamoxifen use;
- Previous invasive cancer.

Groups:

- Anastrozole ($n = 3,125$);
- Tamoxifen ($n = 3,116$);
- Combination ($n = 3,125$, discontinued).

Primary endpoint: Breast cancer DFS.

Secondary endpoints:

- Time to recurrence;
- Incidence of contralateral breast cancer;
- Adverse effect rates for each drug;
- Health-related QoL;
- Bone and lipid effects of each drug.

Mean follow up: 120mo:

Results

- An absolute reduction of recurrence of 2.7% at 5y and 4.3% at 10y was reported for anastrozole, compared with tamoxifen, in the hormone receptor-positive patients. (See Table 21.12.)

Table 21.12 Summary of results

| | Anastrozole ($n = 3,125$) | Tamoxifen ($n = 3,116$) |
|-----------------------------|---|---------------------------|
| Recurrence | 953 (30.5%) HR 0.91, 95% CI 0.83–0.99, $p = 0.04$ | 1,022 (32.8%) |
| All-cause mortality | 734 (23.5%) HR 0.97, 95% CI 0.88–1.08, $p = 0.6$ | 747 (24.0%) |
| Contralateral breast cancer | 73 0.68, 95% CI 0.50–0.91, $p = 0.01$ | 105 |
| Endometrial cancer | 6 (0.2%) OR 0.25, 95% CI 0.08–0.63, $p = 0.001$ | 24 (0.8%) |
| Fractures | 451 (14.4) OR 1.33, 95% CI 1.15–1.55, $p < 0.0001$ | 351 (11.3) |

Discussion

Anastrozole reduced the recurrence of breast cancer (including contralateral breast cancer) and was associated with significantly reduced endometrial cancer. Compared with tamoxifen, anastrozole, an AI, offered no advantage with respect to all-cause mortality. Anastrozole induced bone loss and premature osteoporotic fractures; however, the increased fracture rate with anastrozole did not continue after cessation of treatment.

Problems

- Following unblinding of the study, it is possible that some patients in the tamoxifen arm subsequently received anastrozole.
- The optimum duration for endocrine therapy has yet to be determined, though it is increasingly being extended to 10y.

Herceptin for early breast cancer

HERA (HERceptin Adjuvant trial): Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer.

AUTHORS: Piccart–Gebhart M, Procter M, Leyland–Jones B *et al.*

REFERENCE: *N Engl J Med* (2005) 353, 1659–72.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First RCT to demonstrate that the use of a monoclonal antibody directed against the extracellular domain of the HER2 oncoprotein receptor prevents relapse in HER2-positive breast cancer and improves overall survival by 30%.

Impact

Trastuzumab is now the treatment of choice, after adjuvant chemotherapy, for the 15–25% of patients with early HER2-positive breast cancer. It carries a small risk (<2%) of causing CCF. It has confronted publicly funded health systems with a major challenge of affordability.

Aims

Self-sufficiency in growth signals is one of six molecular ‘hallmarks of cancer’ identified in the late twentieth century. The transmembrane receptor tyrosine kinase HER2/*neu* is overexpressed in up to a quarter of breast cancers where it mediates growth signals and increases the risk of cancer relapse and death. Trastuzumab (Herceptin®) is a monoclonal anti-HER2 antibody that slows the progression of advanced HER2-positive disease. This trial aimed to show that taking trastuzumab for 1–2y after standard chemotherapy could reduce relapse in early disease.

Methods

Patients: 5,081 women from 26 groups and 91 international centres.

Inclusion criteria: Quite broad, compared to USA-based trials:

- Well women with completely excised HER2-positive early breast cancer;
- HER2/*neu* 3+ tumour IHC- or 2+ and fluorescence *in situ* hybridization (FISH)-positive;
- 6mo (≥ 4 cycles) of (neo)adjuvant chemotherapy pre-randomization;
- Either axillary node-positive or node-negative with 1° >1cm;
- Adequate cardiac function (LVEF >55%).

Exclusion criteria: HER2-negative disease or metastatic cancer.

Groups: Trastuzumab dosing = 8mg/kg, then 6mg/kg 3-weekly infusions:

- Observation only (no treatment) ($n = 1,693$);
- 1y of trastuzumab ($n = 1,694$);
- 2y of treatment after adjuvant chemotherapy ($n = 1,694$).

Primary endpoint: DFS.

Secondary endpoints:

- Contralateral breast cancer; second non-breast malignant disease;
- Overall survival;
- Cardiac morbidity (CCF or cardiac death).

Follow-up: Every 3mo for first 2y, then annually from y 2–10. Comprised clinical review and periodic blood tests, chest X-ray, mammogram, ECG, and echocardiogram or multiple-gated acquisition (MUGA) scan for LVEF.

Results**Table 21.13** Summary of results

| Primary endpoint | Observation | 1y trastuzumab | p |
|------------------------------|-------------|----------------|---------|
| 2y DFS | 77% | 86% | <0.0001 |
| Secondary endpoints | | | |
| 2y overall survival | 95% | 96% | ns |
| Symptomatic CCF | 0.1% | 1.7% | <0.001 |
| Contralateral breast cancer | 0.4% | 0.4% | ns |
| Breast cancer related deaths | 2.2% | 1.7% | ns |

Discussion

The first HERA results were released after only 12mo of median F/U, due to a strongly positive gain in DFS for 1y trastuzumab vs observation. On release, around half of the women in the control arm chose to switch to delayed adjuvant trastuzumab. This will confound future analyses of the HERA data, and there will always be some doubt as to the durability of the survival benefit. In a later analysis, at around 2y, the overall survival endpoint reached significance (HR 0.66, $p = 0.01$). The HERA authors point out that the only other agent found to improve overall survival after 2y was tamoxifen, ‘the most successful [systemic] treatment ever developed for breast cancer’. Trastuzumab was associated with cardiac morbidity, with 1.7% experiencing cardiac toxicity vs 0.1% on placebo. The cardiac SEs were accentuated, when given with anthracycline chemotherapy, and require cardiac monitoring for all women. The trial’s third arm of 2y trastuzumab has recently reported no further benefit. At a median F/U of 8y, HR for overall survival of 1y trastuzumab vs observation was 0.76 (0.65–0.88, $p = 0.0005$), despite cross-over of 884 patients from observation to trastuzumab therapy. One year of treatment remains the standard of care. (See Table 21.13.)

Problems

- The UK cost of therapy at £25,000 per patient is expensive, particularly when only 40% of patients will benefit.
- Several large RCTs (e.g. NSABP-B31, N9831, and BCIRG-006) have suggested trastuzumab is more effective, if given concurrently with chemotherapy (as well as following it).
- FinHer (Finland Herceptin) RCT (*N Engl J Med* (2006) **354**, 809–20) ($n = 232$) found a strong DFS benefit for short-course concurrent trastuzumab (stops at the end of chemotherapy, hence is a quarter of the expense). This is being considered by the short-or-long-duration (SOLD) trial.

Breast cancer: bisphosphonates for bone metastasis

Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases.

AUTHORS: Hortobagyi G, Theriault R, Porter L *et al.*

REFERENCE: *N Engl J Med* (1996) 335, 1785–91.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Monthly infusions of pamidronate, given in addition to chemotherapy, can reduce skeletal complications in women with lytic bone metastases from breast cancer.

Impact

Bisphosphonates are now a well-established treatment for women with bone metastases from breast cancer, with newer-generation agents providing even better results.

Aims

Bone metastases occur in most women with advanced breast cancer. The skeletal destruction that develops can lead to pain, immobility, and reduction in QoL. Bisphosphonates inhibit bone resorption by osteoclasts and are often used to treat cancer-related hypercalcaemia. Early trials had suggested that they may reduce skeletal complications in women with breast cancer. This trial aimed to confirm these findings.

Methods

Patients: 382 patients from 97 centres in the USA, Canada, Australia, and New Zealand.

Inclusion criteria:

- Stage IV breast cancer and receiving chemotherapy;
- At least one lytic bone metastasis (≥ 1 cm in diameter);
- ECOG performance score 0–3.

Exclusion criteria:

- Skeletal complications (pathological fracture, need for radiation to bone or bone surgery, spinal cord compression due to vertebral collapse);
- Corrected serum calcium >3 mmol/L in 2wk pre-enrolment;
- Serum creatinine >220 micromol/L;
- Ascites;
- Serum bilirubin >43 micromol/L;
- Heart failure of NYHA classes III/IV;
- Treatment with bisphosphonate in 60d pre-study;
- Treatment with radiation, corticosteroids (except as part of chemotherapy), calcitonin, or plicamycin during 2wk pre-enrolment.

Groups:

- Monthly pamidronate 90mg ($n = 185$);
- Placebo ($n = 197$ patients; two not evaluable).

Primary endpoint: Time to first skeletal complication.

Secondary endpoints:

- Proportion of patients with skeletal complications;
- Bone pain;
- Performance status.

Follow-up: Monthly clinical review and serum calcium measurement. X-ray skeletal surveys at 3, 6, and 12mo.

Results

Table 21.14 Summary of results

| | Pamidronate | Placebo | p |
|--|-------------|---------|-------|
| Median time to first skeletal complication | 13.1mo | 7mo | 0.005 |
| Proportion of patients developing skeletal complications | 43% | 56% | 0.008 |

- Pamidronate significantly reduced bone pain progression, compared with placebo (decreased scores in 44% vs 32%, $p = 0.03$);
- Significantly less deterioration in performance status with pamidronate, compared with placebo ($p = 0.03$). (See Table 21.14.)

Discussion

The response of bone disease to chemotherapy ranged from 0 to 30%. The addition of bisphosphonate had clear benefits, particularly after six cycles of treatment. Hypercalcaemia rates were reduced after three cycles, need for radiotherapy after six, need for surgery after nine, and rate of non-vertebral pathological fractures after 12 cycles. The treatment was well tolerated. Bisphosphonates are now an integral part of the management of breast cancer with bone metastases. Newer bisphosphonates developed since this trial was performed may deliver improved results and can be infused over shorter periods, with oral agents also being available.

Problems

- Fairly stringent exclusion criteria were present. For example, patients with skeletal complications were excluded; this should be considered when extrapolating the significance of these results to patients with complications of their malignancy or pre-existing conditions.

Cardiac surgery

Introduction 592

Coronary artery disease: surgery vs best medical therapy 594

Coronary artery disease: surgery vs angioplasty 596

Coronary artery disease: surgery vs bare-metal stent 598

Coronary artery disease: surgery vs drug-eluting stent 600

Coronary bypass grafts: comparison of arterial vs
venous graft 602

Coronary artery bypass graft: off-pump vs on-pump bypass 604

Valve replacement: mechanical vs biological valve 606

Aortic stenosis: surgery vs transcatheter aortic valve
implantation 608

Introduction

At the end of the nineteenth century, the pre-eminent surgeon of his time Stephen Paget stated that *'surgery of the heart has reached the limit set by nature to all surgery; no new discovery can overcome the natural difficulties that attend a wound of the heart.'* Such conventional wisdom would have stifled uninspired minds. However, a handful of surgical pioneers who were willing to think 'out of the box' and challenge perceived limitations continued to dream that the impossible would one day become a reality.

A little over 50y later, the era of modern heart surgery began in earnest. Stories about pioneering procedures, such as the Blalock–Taussig shunt, cross-over circulation by Lillehei, deep hypothermia by Bigelow, and the heart–lung machine by Gibbon, to name a few, are now treasured classics. The second half of the twentieth century saw advancements in the correction of complex congenital cardiac defects, heart–lung transplantation, and surgery for ischaemic and valvular heart disease.

The establishment of what is now almost regarded as 'routine' cardiac surgery rests not only on the shoulders of surgical giants, but equally on the courage of patients and the trust that they place into the hands of their physicians. It is to these people that we owe our salute.

Coronary artery disease: surgery vs best medical therapy

Eleven-year survival in the Veterans Administration randomized trial of coronary bypass surgery for stable angina.

AUTHORS: The Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group.

REFERENCE: *N Engl J Med* (1984) 311, 1333–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Compared to best medical therapy, CABG improves prognosis in two subgroups of patients with stable angina without left main stem stenosis. The first group (technically high-risk, based upon angiograms) includes those with triple-vessel disease and/or impaired LV function on angiography. The second group (clinically high-risk) includes patients with at least two out of three risk factors (including previous MI, resting ST depression, and history of HTN). The survival advantage is even more pronounced in patients with combinations of the above risks.

Impact

This is the earliest large-scale RCT to demonstrate the superiority of CABG over best medical treatment in selected patient groups. This refinement in the selection of patients who would benefit most from CABG is crucial in ensuring that patients with stable angina receive the most appropriate therapy.

Aims

CAD is subject to varied management. The study was designed to ascertain whether CABG improved survival in patients with chronic stable angina, compared to best medical therapy. The aim was to allocate patients on an ITT basis, thus mimicking real-life clinical decision more closely.

Methods

Patients: 686 patients at 13 centres in the USA.

Inclusion criteria:

- Stable angina for >6mo;
- On medical therapy for >3mo;
- >50% stenosis in ≥ 1 coronary arteries;
- Resting or exercise ECG changes.

Groups:

- CABG ($n = 332$; includes 20 patients who did not have the operation);
- Best medical practice ($n = 354$; including 133 who proceeded to CABG).

Primary endpoint: Death from all causes.

Follow-up: Minimum of 107mo. Mean F/U 11.2y.

Results

Table 22.1 Summary of results

| | CABG | Best medical practice | <i>p</i> |
|---------------------------------|-----------|-----------------------|---------------|
| High-risk, based on angiography | 76% (50%) | 52% (38%) | 0.002 (0.03) |
| Clinically high-risk | 72% (49%) | 52% (36%) | 0.003 (0.02) |
| Combination | 76% (54%) | 36% (24%) | 0.002 (0.005) |

Survival at 7y (in brackets = survival at 11y).

Discussion

CABG was superior to best medical therapy, in terms of long-term prognosis, in patients with triple-vessel disease. The 7y and 11y survival rates were similar across the three categories for patients post-CABG, whereas survival was dramatically lower for patients in the combination category who were treated medically. These results provide the first steps towards a risk stratification model for different patients under consideration for CABG and are extremely useful for patient counselling. (See Table 22.1.)

Problems

- This trial was conducted in the 1970s. Patients undergoing CABG now are considerably older with greater co-morbidities.
- The large numbers of patient cross-over from the medical to the surgical group dilutes the advantages of the original CABG group.

Coronary artery disease: surgery vs angioplasty

BARI (Bypass Angioplasty Revascularisation Investigation): Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease.

AUTHORS: BARI Investigators.

REFERENCE: *N Engl J Med* (1996) 335, 217–25.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In non-diabetic patients with triple-vessel disease, PTCA provides an acceptable alternative to CABG, in terms of 5y survival. However, re-intervention rates in the PTCA group are significantly higher. In patients with DM and multivessel disease, CABG is superior to PTCA, in terms of 5y prognosis.

Impact

This is the largest randomized study to compare PTCA vs CABG in patients with multivessel disease. The 5y results suggest that patients with DM should be referred for CABG, whereas PTCA is a potentially acceptable alternative for suitable non-diabetic patients, although they should be informed of the higher likelihood of need for re-intervention.

Aims

CABG had been demonstrated to result in improved survival for certain subgroups of patients with multivessel CAD. Although initially used for single-vessel disease, less invasive PTCA had been increasingly used in these patients with multivessel disease. This study was designed to ascertain whether PTCA, as an initial treatment in patients with multivessel disease, was comparable to CABG.

Methods

Patients: 1,829 patients at 18 centres in the USA and Canada.

Inclusion criteria:

- Multivessel disease suitable for both PTCA and CABG;
- Severe angina or evidence of ischaemia.

Exclusion criteria:

- Emergency revascularization;
- Left main stem stenosis;
- Prior CABG or PTCA;
- Age >80y;
- Need for concomitant major surgery (e.g. aortic/mitral valve surgery, abdominal aortic aneurysm (AAA) surgery, carotid endarterectomy).

Groups:

- CABG ($n = 914$);
- PTCA ($n = 915$).

Primary endpoint: All-cause mortality.

Secondary endpoints:

- Q-wave MI;
- Need for revascularization.

Follow-up: Average of 5.4y (range 3.8–6.8y).

Results

Table 22.2 Summary of results

| | CABG | PTCA | <i>p</i> |
|-------------------------------------|-------|-------|----------|
| 5y survival (all patients) | 89.3% | 86.3% | 0.2 |
| 5y survival (patients with DM) | 80.6% | 65.5% | 0.003 |
| 5y survival (non-diabetic patients) | 91.4% | 91.1% | 0.7 |
| Re-intervention rate | 8% | 54% | <0.001 |
| 5y cumulative rate of MI | 11.7% | 10.9% | 0.5 |

Discussion

For patients with DM and multivessel disease, CABG was the procedure of choice. In non-diabetic patients with triple-vessel disease, PTCA was an acceptable alternative to CABG, in terms of 5y survival rates. However, PTCA was associated with high rates of repeat revascularization (54%), with ~31% of patients subsequently requiring CABG within 5y. (See Table 22.2.)

Problems

- The high re-intervention rate in the PTCA group was largely attributable to coronary restenosis, following the procedure. With the advent of coronary stents, this study is now largely of historical value, as most PCIs now are accompanied by stent insertions.
- It is conceivable that, with a longer period of F/U, more patients in either group would require repeat procedures, although it is not known whether the increase would be greater in the PTCA or the CABG group. Also the survival advantages of CABG accrue with time.
- See the final bullet point of CABRI study (re: different patient mix).

Coronary artery disease: surgery vs bare-metal stent

SoS (Stent or Surgery) trial: Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease.

AUTHORS: SoS Investigators.

REFERENCE: *Lancet* (2002) **360**, 965–70.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

At a median F/U of 2y, patients with multivessel CAD treated with BMS have a significantly higher repeat revascularization and mortality rate than those undergoing CABG.

Impact

Although angioplasty and stent play an important role in management, CABG ultimately remains the gold standard in the treatment of patients with multivessel CAD.

Aims

Previous RCTs had shown no difference in outcome (in terms of subsequent MI or death) between PTCA and CABG. However, it is likely these studies were underpowered. A subsequent meta-analysis of these early studies concluded PTCA to be associated with poorer outcomes, with both poorer resolution of symptoms and an increased need for repeat procedure. With the use of coronary stent implantation as an adjunct to balloon dilatation reported to improve outcomes of PCI, this trial aimed to compare the clinical outcomes of patients with multivessel CAD treated with either initial BMS or CABG.

Methods

Patients: 988 patients at 53 centres in Europe and Canada.

Inclusion criteria:

- Consensus view of trial surgeon and interventionist that revascularization clinically indicated and appropriate by either strategy;
- Interventionist identified ≥ 1 lesion suitable for stent implantation.

Exclusion criteria:

- Previous thoracotomy;
- Previous coronary revascularization;
- Requiring intervention for pathology of the valves, great vessels, or aorta.

Groups:

- CABG ($n = 500$);
- BMS ($n = 488$).

Primary endpoint: Rate of repeat revascularization.

Secondary endpoints:

- All-cause mortality;
- Death or Q-wave MI;
- Symptoms of angina;
- Cardiac medication requirements;
- LV function.

Follow-up: Median of 2y (range 1–4y).

Results

Table 22.3 Summary of results

| (At 2y) | CABG | BMS | <i>p</i> |
|-----------------------------------|----------------|----------------|-------------------------|
| Revascularization rate | 6% | 21% | <0.001 |
| Mortality | 2% | 5% | 0.01 |
| Q-wave MI | 8% | 5% | Not stated |
| Composite mortality and Q-wave MI | 10% | 9% | 0.8 |
| LVEF (mean at 1y) | 54.8% (SE 0.6) | 55.3% (SE 0.6) | 0.6 (95%CI –1.1 to 2.1) |

Discussion

CABG was superior to BMS for the treatment of patients with multivessel CAD. Patients who underwent CABG had lower incidences of repeat revascularization and lower overall mortality. The higher incidence of MI in the CABG group was mainly observed in the perioperative period. (See Table 22.3.)

Problems

- It is estimated that only 3–6% of the eligible patient population were randomized, leading to an inherent selection bias. Therefore, it might be difficult to extrapolate the findings to the general patient population.
- As in the ARTS trial (*N Engl J Med* (2001) **344**, 1117–24), the majority of patients in the trial had double-vessel disease. It is known from other studies that the patient population benefiting the most from CABG are those with triple-vessel disease. If the trial population contained only patients with triple-vessel disease, the margin of benefit might be even more pronounced, in favour of CABG.

Coronary artery disease: surgery vs drug-eluting stent

SYNTAX (SYnergy between PCI with TAXus and cardiac surgery):

Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial.

AUTHORS: Mohr F, Morice M-C, Kappetein A *et al.*

REFERENCE: *Lancet* (2013) **381**, 629–38.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Overall, CABG remains the standard of care, compared to PCI with drug eluting stents (DES), in patients with multivessel disease and/or left main stem disease. This is especially true in patients with a high SYNTAX score (>32). In patients with a low SYNTAX score (0–22), PCI with DES can be an alternative to CABG.

Impact

The development of the SYNTAX score provides a standardized, objective approach to compare the complexity of coronary lesions. The universal acceptance of a Heart Team concept has allowed a balanced approach to treating patients with multivessel/left main stem disease.

Aims

This is the first large-scale randomized study to compare the relative merits of DES vs CABG in the treatment of patients with multivessel or left main disease. The goal of the SYNTAX score was to allow coronary lesions to be defined and described in a standardized fashion.

Methods

Patients: 1,800 patients at 85 centres in Europe and the USA.

Inclusion criteria: *De novo* triple-vessel disease and/or left main disease deemed suitable for both CABG and PCI, as per consensus view by the Heart Team (cardiac surgeons and interventional cardiologists).

Exclusion criteria:

- Concomitant cardiac surgery required;
- Persisting acute MI;
- Previous PCI or CABG.

Groups:

- CABG ($n = 897$);
- DES ($n = 903$).

Primary endpoint: Composite rate of MACCE, defined as all-cause mortality, repeat revascularization, MI, and stroke at 1y.

Secondary endpoints:

- MACCE rates at 1mo, 6mo, 3y, and 5y;
- Rates of individual MACCE components;
- Rates of stent thrombosis and graft occlusion.

Follow-up: 5y.

Results

Table 22.4 Summary of results

| (At 5y) | SYNTAX score >32 (high) | | | SYNTAX score 23–32 (intermediate) | | | SYNTAX score 0–22 (low) | | |
|----------------------------------|----------------------------|-------|---------|--------------------------------------|-------|--------|----------------------------|-------|-------|
| | CABG | DES | p | CABG | DES | p | CABG | DES | p |
| MACCE | 26.8% | 44.0% | <0.0001 | 25.8% | 36.0% | 0.008 | 28.6% | 32.1% | 0.43 |
| Repeat revascular- ization | 12.1% | 30.9% | <0.0001 | 12.7% | 24.1% | 0.0005 | 16.9% | 23.0% | 0.056 |
| MI | 3.9% | 10.1% | 0.004 | 3.6% | 11.2% | 0.0009 | 4.2% | 7.8% | 0.11 |
| All-cause mortality | 11.4% | 19.2% | 0.005 | 12.7% | 13.8% | 0.68 | 10.1% | 8.9% | 0.64 |
| Stroke | 3.7% | 3.5% | 0.80 | 3.6% | 2.0% | 0.25 | 4.0% | 1.8% | 0.11 |

Discussion

Overall, patients treated with CABG vs DES have lower MACCE (26.9% vs 37.3%), MI (3.8% vs 9.7%), and repeat revascularization (13.7% vs 25.9%; all $p < 0.0001$). All-cause death (11.4% vs 13.9%) and stroke rates (3.7% vs 2.4%) were not significant between the two groups. In patients with a high SYNTAX score, CABG offers superior long-term results, in terms of MACCE, repeat revascularization, MI, and all-cause mortality. In patients with intermediate SYNTAX score, CABG confers advantage, in terms of MACCE, repeat revascularization, and MI. Patients with a low SYNTAX score can be treated with either therapy. (See Table 22.4.)

Problems

The trial was designed to show non-inferiority of PCI with DES vs CABG at the primary endpoint of composite MACCE at 1y. As this non-inferiority was not met at 1y, subsequent subgroup analysis at different time lines should be regarded as observational and hypothesis-generating.

Coronary bypass grafts: comparison of arterial vs venous graft

Cleveland Clinic Study: Influence of the internal-mammary-artery graft on 10-year survival and other cardiac events.

AUTHORS: Loop F, Lytle B, Cosgrove D *et al.*

REFERENCE: *N Engl J Med* (1986) 1, 1–6.

STUDY DESIGN: Observational, retrospective.

EVIDENCE LEVEL: 2b.

Key message

The use of the internal mammary artery (IMA) graft to the left anterior descending (LAD) artery confers superior long-term survival and reduces major adverse cardiac events, compared to the use of vein grafts.

Impact

This landmark paper caused a monumental shift towards the use of the left IMA as the conduit of choice for CABG.

Aims

The conduits used in CABG have different degradation rates. The aim of this study was to determine the influence of the IMA, as compared to a vein graft, on long-term morbidity and mortality after CABG.

Methods

Patients: 5,931 patients at one centre in the USA (first 1,000 patients annually undergoing isolated CABG between 1971 and 1979 were analysed).

Groups:

- IMA group: IMA to anterior descending coronary artery, either alone or with ≥ 1 saphenous vein graft(s) ($n = 2,306$);
- Non-IMA group: saphenous vein graft(s) only ($n = 3,625$).

Inclusion criteria:

- $>50\%$ stenosis of LAD artery \pm disease in other coronary arteries;
- Use of either IMA or vein grafts to LAD \pm grafts to other coronary arteries.

Exclusion criteria:

- Left main stem stenosis $>70\%$;
- Emergency surgery;
- Previous cardiac surgery;
- Bilateral/sequential/free IMA grafts;
- IMA graft to other coronary arteries;
- Perioperative deaths.

Primary endpoint: Survival at F/U.

Secondary endpoints:

- Cardiac re-operations;
- Late MI;
- Hospitalization for cardiac events.

Follow-up: Mean of 8.7y (IMA group: 8.5y, non-IMA group: 8.8y).

Results

Table 22.5 Summary of results

| | IMA group | Non-IMA group | p |
|--|-----------|---------------|---------|
| Primary endpoints (actuarial survival at 10y) | | | |
| Single-vessel disease | 93.4% | 88% | 0.05 |
| Double-vessel disease | 90% | 79.5% | <0.0001 |
| Triple-vessel disease | 82.6% | 71.0% | <0.0001 |
| Secondary endpoints (risk ratios) | | | |
| Cardiac re-operations | 1 | 2.00 | <0.0001 |
| Hospitalization for cardiac events | 1 | 1.25 | <0.0001 |
| Late MI | 1 | 1.41 | <0.0001 |

Discussion

Patients with IMA to LAD grafts had superior 10y survival, as compared to patients receiving vein grafts to the LAD artery. This was especially pronounced in patients with triple-vessel disease. There was also a significant reduction in risk of major adverse cardiac events. (See Table 22.5.)

Problems

- This was an observational study and therefore carried inherent limitations. The authors attempted to correct for patient differences by using statistical modelling to even out potential confounding variables.
- This study was based upon patients operated on in the 1970s. Patient demographics have changed considerably since then.
- The superior results of the IMA graft were based on increased long-term patency. However, with the now routine post-operative use of statins, ACE-Is, antiplatelet agents, and antihypertensive medications, vein graft patency rates may be higher.

Coronary artery bypass graft: off-pump vs on-pump bypass

Octopus trial: A multicentre, randomized study comparing outcomes among patients who underwent coronary artery bypass grafting without the aid of the cardiopulmonary bypass machine (off-pump) vs those who did (on-pump).

AUTHORS: Dijk D, Nierich A, Jansen E *et al.*

REFERENCE: *Circulation* (2001) **104**, 1761–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

At 1mo F/U, off-pump surgery produces equivalent rates of operative survival, freedom from coronary re-intervention, stroke, MI, and QoL, as compared to on-pump surgery.

Impact

Off-pump surgery for CABG is an acceptable alternative to on-pump surgery.

Aims

This study aimed to investigate whether off-pump surgery was safe, with minimal complications and satisfactory early outcomes, as compared to on-pump surgery.

Methods

Patients: 281 patients at three centres in The Netherlands.

Inclusion criteria:

- First-time isolated CABG;
- Off-pump deemed technically feasible.

Exclusion criteria:

- Emergency/concomitant major surgery;
- Poor LV function;
- Q-wave MI in the previous 6wk.

Groups: At randomization:

- Off-pump ($n = 142$; ten converted to on-pump, and one had angioplasty instead);
- On-pump ($n = 139$; five underwent off-pump).

Primary endpoint: Post-operative mortality.

Secondary endpoints: Stroke, MI, coronary re-intervention, and QoL.

Follow-up: Minimum 1mo post-operative F/U.

Results

Table 22.6 Summary of results

| At 1mo | Off-pump | On-pump | <i>p</i> |
|---------------------|----------|---------|----------|
| Primary endpoint | | | |
| Overall mortality | 0% | 0% | ns |
| Secondary endpoints | | | |
| MI | 4.9% | 4.3% | ns |
| Re-intervention | 1.4% | 0% | ns |
| Stroke | 0.7% | 1.4% | ns |
| Overall QoL | 0.69 | 0.71 | ns |

Discussion

Off-pump surgery has gained acceptance as a safe and viable alternative to conventional on-pump surgery. It has distinct advantages in minimizing ascending aorta manipulation during surgery, therefore potentially minimizing atherosclerotic embolization and perioperative stroke. The avoidance of cardiopulmonary bypass may reduce systemic inflammatory responses, potentially avoiding end-organ complications. However, continuous quality improvements have ensured that coronary artery bypass surgery remains low in complications, either with the on- or off-pump techniques. (See Table 22.6.)

Problems

- The patients enrolled in this study had predominantly one- to two-vessel disease. The majority of patients referred for surgery these days have triple-vessel disease. The technical difficulty of the procedure escalates with an increasing number of grafts.
- The patients in this study had normal EF and would therefore be more tolerant of cardiac manipulation with the off-pump technique. Patients with poor LV function are more prone to haemodynamic instability and less likely to tolerate the off-pump procedures.
- Off-pump CABG might potentially be associated with poor-quality anastomosis, due to the need to suture a moving target. The study only had F/U to 1mo, and mid- to late-term complications, such as graft stenosis or occlusions, might not have been picked up.

Valve replacement: mechanical vs biological valve

Edinburgh Valve Study: Twenty year comparison of a Bjork–Shiley mechanical heart valve with porcine bioprostheses.

AUTHORS: Oxenham H, Bloomfield P, Wheatley D *et al.*

REFERENCE: *Heart* (2003) 89, 715–21.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There are no differences in overall survival at 20y between patients receiving either mechanical or biological valves. However, patients receiving mechanical valves are less likely to require re-operation, due to valve failure. This is tempered by the fact that these patients are subject to elevated risks of bleeding from anticoagulation.

Impact

In general, patients are recommended to have a biological valve, if they are either aged >65y and require aortic valve replacement (AVR), or are >70y and require mitral valve replacement (MVR). However, individual patient factors (e.g. preoperative warfarin use, co-morbidities, and personal preference) must be considered.

Aims

A previous long-term comparison of mechanical valves with porcine prosthetic heart valves by the same group had reported significantly higher survival with the Bjork–Shiley (mechanical) prosthesis at a median F/U of 12y, largely due to an increased risk of re-operation due to porcine valve failure beyond 7y. Although the improved survival trend with mechanical valves remained beyond 12y, it was no longer significant. Furthermore, mechanical valves carry the risk associated with long-term anticoagulant use. This paper reported 20y F/U comparisons of morbidity and mortality outcomes in patients receiving either biological or mechanical valve prosthesis for either MVR or AVR.

Methods

Patients: 533 patients (excluding eight patients with tricuspid valve replacement) at one centre in Scotland.

Inclusion criteria: All patients requiring heart valve replacement.

Exclusion criteria: Long-term anticoagulation contraindicated or patient reluctance to take anticoagulation over the long term.

Groups:

- Mechanical prosthesis ($n = 267$: 129 MVR, 109 AVR, 29 AVR and MVR);
- Biological prosthesis ($n = 266$: 132 MVR, 102 AVR, 32 AVR and MVR).

Primary endpoint: Survival (at 20y).

Secondary endpoints:

- Re-operation;
- Bleeding;
- Embolism;
- Endocarditis.

Follow-up: Mean F/U 20.4y. F/U at regular intervals with either clinic visits or mailed questionnaires.

Results

- Demographics (see Table 22.7):
 - Mean age 53.9y (mechanical group 54.4y; biological group 53.4y);
 - Six patients lost to F/U;
 - 56% ($n = 296$) ♀;
 - 7.5% ($n = 40$) had previous valve replacement.

Table 22.7 Summary of results

| At 20y | Mechanical | Biological | <i>p</i> |
|---------------------------|------------|------------|----------|
| AVR survival | 28.4% | 31.3% | 0.6 |
| MVR survival | 22.4% | 18.4% | 0.4 |
| Re-operation | 12.2% | 67.8% | <0.0001 |
| Bleeding (major episodes) | 40.7% | 27.9% | 0.008 |
| Embolism | 36.6% | 37.9% | 0.8 |
| Endocarditis | 7.5% | 10.3% | 0.6 |

Discussion

This trial served to provide quantitative data with which to inform patients undergoing valve replacement, with regard to choice of prosthesis. Although mechanical valves are known to be practically free from structural deterioration over a patient's lifetime, there was a cumulative risk of major bleeding episodes of 1% per year. Biological prostheses are prone to structural deterioration over time (mitral > aortic). The death from re-operation has progressively improved over the years and, for first-time aortic valve re-operation, was observed as approaching an acceptable 5%. Therefore, individual patient factors must be considered for the choice of prosthesis.

Problems

- Patient demographics have changed considerably, since the initiation of this trial in the 1970s. Patients are now older, when they undergo valve replacement (mean age >65y). There are also fewer patients with rheumatic mitral valve disease requiring replacement. The majority of mitral valve surgery repairs follow myxomatous valve changes.
- There have been advances in the fixation and anti-calcification technologies of newer-generation biological prostheses, with longer freedom from structural deterioration. Therefore, there is a lower likelihood of the need for re-operation in this group.

Aortic stenosis: surgery vs transcatheter aortic valve implantation

PARTNER (Placement of AoRtic TraNscathetER valve): Two-year outcomes after transcatheter or surgical aortic-valve replacement.

AUTHORS: Kodali S, Williams M, Smith C *et al.*

REFERENCE: *N Engl J Med* (2012) 366, 1686–95.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In high-risk surgical patients (predicted mortality at 30d of $\geq 15\%$ and/or STS (Society of Thoracic Surgeons) score of ≥ 10) with severe aortic stenosis, surgical AVR currently remains the gold standard. However, transcatheter aortic valve implantation (TAVI) can be considered a viable alternative.

Impact

The development of TAVI has revolutionized the treatment of inoperable patients with severe aortic stenosis. Extending the indication for TAVI to high-risk surgical patients can now be reasonably considered.

Aims

The treatment of patients with severe aortic stenosis and multiple comorbidities remains a huge challenge. This trial examines the efficacy and safety of TAVI vs surgical AVR in the treatment of high-risk patients with severe aortic stenosis.

Methods

Patients: 699 patients at 25 centres.

Inclusion criteria:

- Severe symptomatic aortic stenosis (aortic valve area $\leq 0.8\text{cm}^2$, peak velocity 4ms^{-1} or greater, mean valve gradient $\geq 40\text{mmHg}$);
- High surgical risk (predicted 30d mortality of $\geq 15\%$ and/or STS score ≥ 10 or greater);
- NYHA score ≥ 2 .

Exclusion criteria:

- Acute MI $\leq 30\text{d}$;
- Aortic valve is unicuspid, bicuspid, or non-calcified;
- Serum creatinine $> 3.0\text{mg/dL}$ or dialysis;
- LVEF $< 20\%$;
- Aortic annulus $< 17\text{mm}$ or $> 25\text{mm}$;
- Any cardiac procedure (except balloon aortic valvotomy) within 30d (or DES within 6mo);
- Severe aortic regurgitation or mitral regurgitation (≥ 3) or prosthetic valve;

- Untreated CAD requiring revascularization;
- Haemodynamic instability;
- CVA or TIA within 6mo;
- Life expectancy <12mo;
- Aortic aneurysm or severe iliofemoral disease;
- Upper GI bleed within past 3mo.

Groups: 1:1 randomization:

- AVR ($n = 351$);
- TAVI ($n = 348$).

Primary endpoint: All-cause mortality at 1y.

Secondary endpoints:

- CV mortality;
- Stroke;
- Repeat hospitalization;
- NYHA functional class;
- Major bleeding;
- Major vascular complications;

Follow-up: 2y.

Results

Table 22.8 Summary of results

| At 2y F/U | AVR | TAVI | <i>p</i> |
|--|-------|-------|----------|
| All-cause mortality | 35.0% | 33.9% | 0.78 |
| CV mortality | 20.5% | 21.4% | 0.80 |
| Stroke and TIAs | 6.5% | 11.2% | 0.05 |
| Repeat hospitalization | 21.7% | 24.7% | 0.41 |
| Mean NYHA class | 1.70 | 1.72 | 0.87 |
| Moderate/severe paravalvular regurgitation | 0.9% | 6.9% | <0.0001 |

Discussion

Overall, patients treated with AVR vs TAVI have similar all-cause mortality, CV mortality, repeat hospitalization rate, and improvement in NYHA functional class. There was an increase in neurological events in the TAVI group, driven primarily by an increased incidence of TIA (major strokes rates remained similar). There was a greater risk of moderate to severe paravalvular leak in the TAVI group, which was associated with an increase in late mortality. (See Table 22.8.)

Problems

The study population was elderly (mean age 84.1 ± 6.6 y). It is not sure if the results would remain similar in younger patients with high surgical risk. The medium- to long-term results of TAVI are not yet established, and extending the indications to patients with moderate surgical risk remains part of an ongoing trial.

Gastrointestinal and hepatobiliary surgery

- Introduction 612
- Gastro-oesophageal reflux: medical vs surgical management 614
- Gastro-oesophageal reflux: type of antireflux surgery 616
- Oesophageal cancer: neoadjuvant chemotherapy 618
- Gastro-oesophageal cancer: perioperative chemotherapy 620
- Gastric cancer: D1 vs D2 resection 622
- Cholecystectomy: timing of surgery 624
- Acute gallstone pancreatitis: endoscopic treatment 626
- Acute pancreatitis: prophylactic antibiotics 628
- Pancreatic cancer: adjuvant therapy 630
- Colorectal cancer: screening 632
- Colorectal cancer: open vs laparoscopic surgery 634
- Colorectal cancer: anti-angiogenic treatment 636
- Rectal cancer: total mesorectal excision 638
- Rectal cancer: neoadjuvant radiotherapy 640
- Rectal cancer: long-course chemoradiotherapy 642
- Hernia repair: type of surgery 644
- Perioperative care: enhanced recovery 646

Introduction

Increasing specialization within general surgery has allowed the firm establishment of upper GI, colorectal, and hepatobiliary surgery as distinct and separate disciplines. Each subspecialty has evolved and subsequently faced the challenge of improving its outcomes, both in the fields of benign and malignant disease.

In cancer treatment, the multidisciplinary approach has developed to become standard, and the evidence base reflects this, now routinely incorporating neoadjuvant and adjuvant oncological treatments, resulting in significant advances in both survival and DFS.

Compared to 20y ago, for example, resection of colorectal liver metastases is now commonplace, with low morbidity and mortality, and 5y survival rates approaching 50%.

In this chapter, we will be looking at the clinical evidence that underpins the main advances in treatment in these three major subspecialties.

Gastro-oesophageal reflux: medical vs surgical management

LOTUS: Laparoscopic antireflux surgery vs esomeprazole treatment for chronic gastro-oesophageal reflux disease.

AUTHORS: Galmiche J, Hatlebakk J, Attwood S *et al.*

REFERENCE: *JAMA* (2011) 305, 1969–77.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Most patients with gastro-oesophageal reflux disease (GORD) will remain in remission for up to 5y with both modern forms of antireflux therapy (either laparoscopic antireflux surgery or drug-induced acid suppression).

Impact

The choice of therapy (surgery or medication) should be tailored to the patient in terms of their co-morbidities, concomitant medication, and individual concerns.

Aims

This study aimed to compare laparoscopic Nissen fundoplication (performed to a standardized protocol in dedicated surgical centres) with updated medication therapy for GERD (cf. British spelling used elsewhere - gastro-oesophageal reflux disease, GORD). The aim was to reflect developments in the surgical approach (laparoscopic as opposed to open) and improved sustained acid suppression agents (esomeprazole instead of omeprazole.)

Methods

Patients: 554 patients across 11 European centres.

Inclusion criteria:

- Patients with GORD who responded to initial 3mo run-in period of treatment with 40mg of esomeprazole;
- At time of randomization, had oesophagitis of no more than Los Angeles (LA) grade B and GORD symptoms no more than mild.

Groups:

- Esomeprazole (20mg od, adjustable to 40mg od after 8wk if not controlled, and then 20mg bd if still symptomatic ($n = 266$);
- Laparoscopic antireflux surgery (LARS)—Nissen fundoplication by a standardized method ($n = 288$).

Primary endpoint: Time to treatment failure (for LARS, defined as need for acid suppressive therapy; for esomeprazole, inadequate symptom control after dose adjustment), expressed as estimated remission rates and analysed using the Kaplan–Meier method.

Follow-up: 6-monthly clinic visits with standardized assessment of GORD symptoms, HRQOL questionnaire, and GORD symptom rating scale. Endoscopy at 1, 3, 5y.

Results

- Estimated remission rates at 5y were 92% in the esomeprazole group, and 85% in the surgery group (log rank $p = 0.048$);
- This difference was no longer significant when best-case scenario modelling for study dropout was addressed;
- Acid regurgitation was less in the surgery group, compared to the esomeprazole group (2% vs 13%, $p \leq 0.001$), whereas dysphagia (11% vs 5%, $p \leq 0.001$), bloating (40% vs 28%, $p \leq 0.001$), and flatulence (57% vs 40%, $p \leq 0.001$) were commoner after surgery;
- There was no difference in serious adverse events.

Discussion

This large multicentre RCT demonstrated that most patients remain in remission at 5y, following both forms of accepted antireflux therapy. Both groups were well matched for demographics and baseline symptoms, and a 3mo run-in period allowed baseline recordings and verification of symptom response to esomeprazole. The high remission rates were due to superior acid suppression of esomeprazole, compared to other medical therapies used in previous trials, as well as the optimized dosing regimen used in the medical group and the use of high-volume specialist centres for the surgical group.

Problems

- Only patients with mild GORD and a response to esomeprazole were included. Therefore, results can be applied to patients with GORD who are controlled on medication but may wish to consider surgery. It cannot be applied to partial or non-responders.
- Only carefully evaluated patients were operated on by experienced surgeons in large-volume academic units; therefore, inferior results may occur in other surgical centres or less well-evaluated patients.
- This was an exploratory study and not designed as a superiority or equivalence trial.

Gastro-oesophageal reflux: type of antireflux surgery

Randomized controlled trial of laparoscopic versus open fundoplication: blind evaluation of recovery and discharge period.

AUTHORS: Nilsson G, Larsson S, Johnsson F.

REFERENCE: *Br J Surg* (2000) **87**, 873–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First double-blind RCT to show an improved short-term outcome following laparoscopic fundoplication, compared with an open procedure, in patients with GORD.

Impact

Laparoscopic fundoplication is now considered the procedure of choice for patients with refractory GORD who require surgery.

Aims

GORD is the commonest upper GI disease in the West, and open antireflux surgery has been shown to have good and long-lasting results. This trial was designed to determine whether laparoscopic fundoplication had any advantages over the open procedure, in terms of speed of post-operative recovery and time for return to work.

Methods

Patients: 60 patients from one centre in Sweden.

Inclusion criteria:

- Refractory GORD confirmed with 24h pH monitoring;
- No previous upper abdominal surgery.

Groups:

- Laparoscopic 360° posterior fundoplication ($n = 30$);
- Open 360° posterior fundoplication ($n = 30$).

Five patients assigned to the laparoscopic group underwent conversion to an open procedure (four of them due to intraoperative complications), and they were analysed separately (not an ITT analysis).

Endpoints:

- Operating time;
- Pain scores and requirement of analgesics;
- Nausea scores and requirement of antiemetics;
- Respiratory function (forced expiratory volume, FEV; and FVC);
- Length of hospital stay;
- Duration of sick leave.

Follow-up: Twice a day until discharge from hospital, and once a week after discharge until the patient returned to work. The type of operation was unknown to the patients and hospital staff.

Results

Table 23.1 Summary of results

| Endpoints | Laparoscopic* (n = 25) | Open* (n = 30) | p |
|-----------------------------------|------------------------|----------------|---------|
| Operating time (min) | 148 (99–208) | 109 (75–174) | <0.0001 |
| Morphine (mg/hospital stay) | 34 (0–216.4) | 67 (25–360) | <0.001 |
| Antiemetics (doses/hospital stay) | 0 (0–3) | 1 (0–9) | 0.1 |
| FEV at d 1 (L) | 2.6 (1.1–5.2) | 2 (0.9–3.4) | 0.008 |
| Hospital stay (d) | 3 (2–6) | 3 (2–10) | 0.02 |
| Sick leave (d) | 27 (13–139) | 32 (7–126) | ns |

* Values represent medians (range). NB. Five patients in the laparoscopic group converted to open procedure.

Discussion

Laparoscopic antireflux surgery has gained popularity, based on the results of observational studies published by specialist centres. This was one of the first RCTs to show that the laparoscopic approach had some modest short-term benefits, compared with open antireflux surgery. In the UK, laparoscopic fundoplication is now widely accepted as the procedure of choice for severe GORD that does not respond to medical treatment. (See Table 23.1.)

Problems

- Small numbers: designed to include only 30 patients in each arm. The analysis was not performed on an ITT basis.
- In this trial, the advantages of the laparoscopic approach, in terms of post-operative pain and duration of hospital stay/sick leave, were more modest than expected. Indeed, other randomized studies have failed to demonstrate any benefits at all, compared with the open procedure.
- Only the short-term outcome of laparoscopic fundoplication was assessed in this trial. Other studies have since shown that laparoscopic antireflux surgery is at least as effective and durable as its open counterpart, in terms of reflux control, and is associated with a good functional outcome overall.
- Four patients assigned to the laparoscopic group in this study suffered from significant intraoperative complications. Other non-randomized studies have also reported some rare, but serious, complications, including major vascular injuries and oesophageal perforations. However, the overall operative morbidity of laparoscopic fundoplication remains low and reduces further with increasing experience of the procedure.

Oesophageal cancer: neoadjuvant chemotherapy

Surgical resection with or without preoperative chemotherapy in oesophageal cancer.

AUTHORS: Medical Research Council Oesophageal Cancer Working Group.

REFERENCE: *Lancet* (2002) 359, 1727–33.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First large RCT to show that preoperative chemotherapy improves survival in patients with resectable oesophageal cancer.

Impact

In the UK, preoperative chemotherapy is now routinely considered for the majority of patients with resectable oesophageal cancer.

Aims

In spite of recent advances in the diagnosis and management of oesophageal cancer, the majority of patients who undergo surgery with curative intent develop locoregional recurrences or distant metastases within 2y of surgery. This trial was designed to determine whether a combination of systemic preoperative chemotherapy and surgery could improve the outcome of these patients, compared with surgical resection alone.

Methods

Patients: 802 patients from 42 European centres.

Inclusion criteria:

- Resectable, histologically confirmed carcinoma of the oesophagus (regardless of histological type or anatomical site);
- No other previous or concomitant malignancy;
- No evidence of cervical lymphadenopathy or other metastases;
- No contraindication to surgery or chemotherapy.

Groups:

- CS group: Immediate preoperative chemotherapy (two 4d cycles, 3wk apart, of cisplatin and fluorouracil), followed by surgical resection ($n = 400$);
- S group: Immediate surgical resection ($n = 402$).

Local clinicians decided the type of surgical procedure and could choose to give preoperative RT to all their patients, irrespective of randomization.

Primary endpoint: Survival time.

Secondary endpoints: Dysphagia and performance status.

Follow-up: On completion of treatment; at 3, 6, 9, and 12mo from randomization; then 6-monthly until death. Analysis by ITT. Median F/U for survivors 36.9mo (CS) and 37.9mo (S).

Results

Table 23.2 Summary of results

| Primary endpoints | CS group | S group | p |
|-----------------------------|---------------|---------------|---------------|
| Survival rate at 2y | 43% | 34% | 0.004* |
| Median survival | 512d (16.8mo) | 405d (13.3mo) | 95% CI 30–196 |
| Secondary endpoints | | | |
| Worsened dysphagia | 8% | 5% | >0.05 |
| Worsened performance status | 24% | 17% | >0.05 |

* For overall survival.

Discussion

This trial was the first to demonstrate that two cycles of neoadjuvant cisplatin and fluorouracil significantly improved survival in patients with localized oesophageal cancer who underwent surgical resection. Subgroup analysis also showed that chemotherapy was equally effective, regardless of histology, tumour site, age, or sex. Preoperative chemotherapy is now considered actively for the majority of patients with resectable oesophageal cancer in the UK. (See Table 23.2.)

Problems

- Modest doses of cisplatin and fluorouracil were used in this trial, in an attempt to reduce toxicity and morbidity prior to major surgery and in order to increase compliance. There is evidence that higher doses of these agents and the addition of other chemotherapeutics, such as epirubicin, can improve survival even further.
- No specific surgical protocol was prescribed in this trial. It has been argued that at least part of the apparent beneficial effect of chemotherapy may be due to suboptimal surgery (e.g. lack of systematic lymphadenectomy). Indeed, a large North American trial of similar design that used a stricter surgical protocol and the same chemotherapeutic agents in higher doses failed to demonstrate survival benefit in the chemotherapy plus surgery group.
- This trial recruited patients with resectable oesophageal cancer, regardless of their preoperative staging, and subgroup analysis by tumour stage was not carried out. Most clinicians believe that the benefit of chemotherapy is minimal for patients with early T1N0 tumours and can be omitted. The majority of these cases are surveillance-detected adenocarcinomas on a background of Barrett's oesophagus.

Gastro-oesophageal cancer: perioperative chemotherapy

MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial: Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.

AUTHORS: Cunningham D, Allum W, Stenning S *et al.*

REFERENCE: *N Engl J Med* (2006) 355, 11–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First RCT to show that perioperative chemotherapy is associated with significantly improved progression-free survival (PFS) and overall survival in patients with resectable gastric cancer.

Impact

Although not previously favoured in the UK, perioperative chemotherapy is now considered routinely for patients with operable (stages II and III) gastric or lower oesophageal adenocarcinoma.

Aims

Surgery for locally advanced gastric and lower oesophageal tumours has variable outcomes. The 'ECF' (epirubicin, cisplatin, and 5-fluorouracil (5-FU)) chemotherapy regime alone had been demonstrated to improve survival. This trial was designed to determine whether three cycles of ECF given before and after surgery, with curative intent, could improve outcomes.

Methods

Patients: 503 patients from 56 international centres (mainly the UK).

Inclusion criteria:

- Histologically confirmed adenocarcinoma of the stomach/lower oesophagus;
- \geq stage II, with no evidence of distant metastases/locally advanced inoperable disease;
- WHO performance status of 0 or 1;
- No previous chemotherapy/RT.

Groups: Surgery in both included oesophagogastrectomy or total/distal gastrectomy, depending on the tumour site. Extent of lymphadenectomy decided by the treating surgeon:

- S: Surgical resection alone ($n = 253$);
- CSC: Perioperative chemotherapy (three pre- and three post-operative cycles of IV ECF) and surgery ($n = 250$).

Primary endpoint: Overall survival.

Secondary endpoints: PFS, surgical and pathological assessments of downstaging, and QoL.

Follow-up: Final analysis when either 320 patients (or ~90%) had died or had F/U for minimum of 2y. Median F/U 49mo (CSC) and 47mo (S).

Results

Table 23.3 Summary of results

| Endpoints | CSC group | S group | p |
|--------------------------|-----------|---------|-------|
| Overall survival (at 5y) | 36.3% | 23% | 0.008 |
| T1 and T2 tumours | 51.7% | 36.8% | 0.002 |
| Curative resection | 79.3% | 70.3% | 0.03 |

- The CSC group had significantly higher likelihood of DFS (HR 0.66, 95% CI 0.53–0.81, $p < 0.001$) and overall survival (HR 0.75, 95% CI 0.59–0.93, $p = 0.008$); 13% increase in 5y survival; 25% decrease in risk of death (see Table 23.3);
- Similar incidence of post-operative complications and 30d mortality.

Discussion

In patients with resectable tumours, perioperative ECF reduced tumour size and stage, significantly improving DFS and overall survival, vs surgery alone. No increase in perioperative morbidity or mortality was observed. The treatment effect was similar, regardless of age, sex, performance status, and 1° tumour site. In many centres, the treatment of metastatic gastric cancer now involves replacing infusional 5-FU with an oral alternative capecitabine; this may make the regimen more attractive to patients and avoids the risks associated with Hickman lines. In addition, studies are being conducted, replacing nephrotoxic cisplatin (given over several hours with high fluid loads) with non-nephrotoxic oxaliplatin (can be given quickly and may improve convenience and efficacy). A follow-on study (UK NCRI ST03) will randomize patients to perioperative chemotherapy with either ECX (epirubicin, cisplatin, and capecitabine) or ECX plus the vascular endothelial growth factor (VEGF) receptor inhibitor bevacizumab, an antibody that has shown encouraging results in other tumour types, including colorectal and lung.

Problems

- The study was originally designed for patients with gastric cancer only. Due to lower-than-anticipated recruitment rates, eligibility criteria were extended to include patients with lower oesophageal adenocarcinomas.
- Several other studies using a variety of neoadjuvant or adjuvant regimens of chemotherapy, with or without RT, have failed to demonstrate such significant survival benefits.
- Reported 5y survival of 23% in the 'surgery only' group is relatively low, compared with the results of non-randomized studies from specialist centres in Japan and the West. In most of these centres, extensive D2 lymphadenectomy is routinely performed for gastric cancer.
- Only 42% of those assigned to receive chemotherapy completed three post-operative cycles. The post-operative component of the regimen may be poorly tolerated, conferring no additional benefits; therefore, many clinicians are inclined to omit it.

Gastric cancer: D1 vs D2 resection

Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial.

AUTHORS: Cuschieri A, Weeden S, Fielding J *et al.*

REFERENCE: *Br J Cancer* (1999) **79**, 1522–30.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This large RCT shows the classical Japanese D2 resection to offer no survival advantage over the less extensive D1 resection in patients with gastric cancer.

Impact

Routine distal pancreatectomy and splenectomy, as an integral part of D2 resection for middle and upper third gastric tumours, have now been abandoned, even by the proponents of D2 surgery. The value of extended (D2) lymphadenectomy is still debated.

Aims

Despite low 5y survival rates, surgery is the only proven effective therapy for gastric carcinoma. Observational studies from Japan and selected specialist Western centres have reported impressive results following D2 resections for potentially curable gastric cancer. This MRC trial was designed to determine whether the apparent superiority of D2 surgery could be confirmed in an RCT.

Methods

Patients: 400 patients from 32 surgeons at multiple centres in Europe.

Inclusion criteria:

- Age >20y;
- Histologically proven and potentially curable gastric cancer;
- No contraindication to major surgery and no other malignancy.

Groups: Type of gastrectomy (total or subtotal), determined according to the site of the 1° tumour:

- D1 resection: Included removal of lymph nodes within 3cm of the tumour ($n = 200$);
- D2 resection: Included removal of the second tier of lymph nodes (N2) in all cases, and pancreaticosplenectomy for middle and proximal-third tumours ($n = 200$).

Primary endpoint: Overall survival.

Secondary endpoints:

- Post-operative morbidity and mortality;
- Effect of lymphadenectomy on survival;
- Effect of pancreatectomy and splenectomy on survival.

Follow-up: At regular intervals until death or until study conclusion. Median F/U 6.5y. ITT analysis was conducted.

Results

- Overall 5y survival rates similar in the two arms (35% for D1 and 33% for D2; $p = 0.4$). Disease-specific survivals and survivals after exclusion of operative deaths also similar ($p > 0.05$);
- Post-operative morbidity and mortality significantly higher in the D2 group, compared with the D1 group (46% vs 28% for morbidity, $p = 0.001$; and 13% vs 6.5% for mortality, $p = 0.04$);
- Subgroup analysis showed that inclusion of distal pancreatectomy and perhaps splenectomy in the resection adversely affected the overall survival of the patients. Furthermore, it provided evidence that extended D2 lymphadenectomy without pancreatectomy or splenectomy may be superior to D1 resection, in terms of long-term survival.

Discussion

This trial failed to reproduce the impressive results reported in case series from Japan for D2 resections, and its findings are very similar to those reported in a Dutch trial of similar design. It is noteworthy that, although overall survival was similar in the two arms of the trial, further analysis of the data provided some evidence that D2 resection without pancreatectomy and splenectomy may be associated with improved long-term survival, compared with the standard D1 resection.

Problems

- Deficient quality control: it is impossible to ascertain whether the operating surgeons were performing true 'Japanese style' D2 resections or not. In fact, there is evidence of significant 'non-compliance and contamination' in relation to the extent of lymphadenectomy, i.e. some patients assigned to D2 resection had less radical dissection, and some patients assigned to D1 resection had more extensive dissection, making interpretation of the value of lymphadenectomy problematic.
- In accordance with the prescribed protocol, all patients with middle and proximal-third tumours assigned to D2 group underwent distal pancreatectomy and splenectomy. This and other studies have shown that inclusion of these procedures is associated with increased post-operative mortality and reduced overall survival. They are no longer considered integral parts of D2 resections, unless there is direct tumour invasion.
- In this study, the reported overall survival for D2 resections was much lower, and the reported post-operative mortality was much higher than the respective figures reported in retrospective studies from Japan and specialist centres in the West.

Cholecystectomy: timing of surgery

Prospective randomized study of early versus delayed laparoscopic cholecystectomy for acute cholecystitis.

AUTHORS: Lo C, Liu C, Fan S *et al.*

REFERENCE: *Ann Surg* (1998) 227, 461–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First RCT to show that early laparoscopic cholecystectomy for acute cholecystitis has significant medical and socio-economic advantages, compared with conservative initial management followed by interval cholecystectomy.

Impact

In specialist centres, laparoscopic cholecystectomy within 72h of admission is now the preferred approach for the management of patients with acute cholecystitis.

Aims

In the pre-laparoscopic era, randomized studies had shown that early open cholecystectomy for acute cholecystitis was safe and associated with shorter total hospital stay and faster recovery. This trial was undertaken, in order to determine whether the same advantages would apply following the introduction of laparoscopic techniques.

Methods

Patients: 99 patients at a single centre in Hong Kong.

Inclusion criteria:

- Clinical picture consistent with acute cholecystitis associated with leukocytosis and/or ultrasonic evidence of acute inflammation;
- Patients presenting within 7d from the onset of their symptoms and considered to be fit for laparoscopic surgery;
- No evidence of spreading peritonitis, no concomitant malignancy or pregnancy, and no previous upper abdominal surgery.

Groups:

- Early: Laparoscopic cholecystectomy within 72h of admission ($n = 45$);
- Delayed: Initial conservative management, followed by laparoscopic cholecystectomy within 8–12wk ($n = 41$).

Endpoints:

- Conversion rate to open procedure (calculation of statistical power of study based upon this);
- Operative time;
- Failure of conservative management;
- Complication rate;
- Length of total hospital stay and recuperation time.

Follow-up: At 1wk post-hospital discharge, and every 4wk thereafter.

Results

Table 23.4 Summary of results

| Endpoint | Early | Delayed | p |
|---------------------------|--------------|--------------|--------|
| Conversion rate (to open) | 11% | 23% | 0.2 |
| Operative time (min)* | 135 (75–220) | 105 (50–290) | 0.02 |
| Complication rate | 13% | 29% | 0.07 |
| Total hospital stay (d)* | 6 (2–16) | 11 (5–33) | <0.001 |
| Recuperation period (d)* | 12 (3–30) | 19 (5–59) | <0.001 |

* Values represent medians (range).

- Four patients in the early group and nine patients in the delayed group were excluded after randomization, for a variety of reasons;
- Eight patients in the delayed group required urgent surgery. Seven of the remaining 33 were readmitted with recurrent symptoms (one required urgent surgery). (See Table 23.4.)

Discussion

Previous non-randomized studies indicated that early laparoscopic cholecystectomy in patients with acute cholecystitis was associated with high conversion rates and increased morbidity. The data from this study suggested, for the first time, that early laparoscopic cholecystectomy (within 72h of admission) was not only feasible and safe, but was also associated with a significantly shortened total hospital stay and recuperation period.

Problems

- This trial was relatively small, and a significant number of patients were withdrawn after randomization. However, subsequent randomized studies have confirmed its main findings.
- The authors commented that laparoscopic cholecystectomy following acute cholecystitis was more difficult (regardless of the timing of the procedure), and a modification of the standard technique was often required. They suggested that these procedures should only be undertaken by experienced laparoscopic surgeons.
- Surgeons in the UK have been slow to adopt a policy of early surgery in patients with acute cholecystitis, mainly because of the logistical problems that such a policy would pose. Elective lists are fully booked well in advance; access to the emergency list for semi-urgent cases can be problematic, and, as mentioned previously, an experienced laparoscopic surgeon would have to be available at all times.

Acute gallstone pancreatitis: endoscopic treatment

Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones.

AUTHORS: Neoptolemos J, London N, James D *et al.*

REFERENCE: *Lancet* (1988) 2, 979–83.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

First RCT to show improved outcome in patients with acute gallstone pancreatitis who undergo early endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy, compared with those who have conservative management.

Impact

ERCP and sphincterotomy, within 48–72h of admission, is now included in the treatment algorithm for patients with predicted severe acute pancreatitis 2° to gallstones, particularly when there is evidence of persistent biliary obstruction.

Aims

Acute pancreatitis is a potentially lethal complication of gallstones. To date, very few treatments or interventions (other than supportive measures) have been shown to modify its natural history. This trial was designed to determine whether urgent ERCP and sphincterotomy could reduce the morbidity and mortality of acute gallstone pancreatitis.

Methods

Patients: 121 patients at a single centre in the UK.

Inclusion criteria:

- Age >18y;
- Serum amylase >1000IU/L and compatible clinical picture;
- Suspected gallstones on ultrasound and biochemistry;
- No other identifiable cause of pancreatitis.

Groups:

- ERCP and sphincterotomy within 72h of admission ($n = 59$);
- Conservative management ($n = 62$).

Patients in both groups were classified as having predicted 'mild' or 'severe' attack, using modified Glasgow (Imrie) criteria (*Gut* (1984) 25, 1340–6).

Endpoints:

- Morbidity and mortality;
- Length of hospital stay;
- Subgroup analysis, according to the predicted severity of the attack.

Results

Table 23.5 Summary of results

| Endpoints | Early ERCP | No early ERCP | <i>p</i> |
|-------------------------------|------------|---------------|----------|
| Mortality | | | |
| Overall | 2% | 8% | ns |
| Predicted mild | 0 | 0 | — |
| Predicted severe | 4% | 18% | ns |
| Complications | | | |
| Overall | 17% | 34% | 0.03 |
| Predicted mild | 12% | 12% | ns |
| Predicted severe | 24% | 61% | <0.01 |
| Hospital stay (median) | | | |
| Predicted mild | 9d | 11d | ns |
| Predicted severe | 9.5d | 17d | 0.03 |

- ERCP successfully completed in 88% of cases. Only one procedure-related complication occurred. (See Table 23.5.)

Discussion

This trial was the first to demonstrate that urgent ERCP and sphincterotomy during an attack of acute gallstone pancreatitis was not only feasible and safe, but also improved the outcome of patients with predicted severe attacks. Although the observed reduction in mortality did not reach statistical significance, there was a significant reduction in the overall incidence of complications and a significant reduction in the length of hospital stay for patients with predicted severe attacks of pancreatitis, who underwent early ERCP and sphincterotomy.

Problems

- Ten patients were excluded from analysis after randomization, because an alternative diagnosis was made (not by ITT analysis). Fifteen more patients who were included in the final analysis did not have the diagnosis of gallstones confirmed on subsequent investigations.
- Patients with predicted mild, as well as predicted severe, attacks were recruited. This and subsequent studies have demonstrated that only patients with predicted severe attacks benefit from early ERCP and sphincterotomy; patients with evidence of persistent biliary obstruction benefit the most.
- A treatment protocol that includes early ERCP and sphincterotomy would require an abdominal ultrasound scan being performed within 24h of admission in all cases, and an experienced endoscopist being available 7d a week. These facilities may not always be available in hospitals that treat patients with acute gallstone pancreatitis.

Acute pancreatitis: prophylactic antibiotics

Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial.

AUTHORS: Isenmann R, Runzi M, Kron M *et al.*

REFERENCE: *Gastroenterology* (2004) **126**, 997–1004.

STUDY DESIGN: RCT

EVIDENCE LEVEL: 1b

Key message

To date, this is the only double-blind, placebo-controlled RCT to investigate the role of antibiotics in acute pancreatitis. It shows that prophylactic antibiotics do not improve outcomes in patients with predicted severe acute pancreatitis.

Impact

This well-designed trial provided evidence against the routine use of prophylactic antibiotics in patients with predicted severe acute pancreatitis, a common practice in the UK.

Aims

Previous trials of antibiotic prophylaxis in the management of acute pancreatitis have been inconclusive, due to inadequate power or poor design. This trial used, for the first time, double-blind methodology to determine whether a combination of prophylactic IV antibiotics could improve the outcome of patients with predicted severe acute pancreatitis, compared with placebo.

Methods

Patients: 114 patients from 19 centres in Germany.

Inclusion criteria:

- Abdominal pain of <72h duration, in combination with a 3-fold elevation of serum amylase or lipase; and
- CRP >150mg/L or evidence of pancreatic necrosis on CT.

Groups: Study medication changed to open antibiotic treatment, when there was evidence of systemic clinical deterioration:

- Antibiotics: Ciprofloxacin (400mg bd IV) plus metronidazole (500mg bd IV) for up to 21d ($n = 58$);
- Placebo: For up to 21d ($n = 56$).

Primary endpoint: Incidence of infected pancreatic necrosis confirmed by operative smears or by fine-needle aspiration.

Secondary endpoints:

- Mortality rate;
- Incidence of local and systemic complications. A Clinical Severity Score (CSS) was devised to assess the magnitude of systemic complications;

- Incidence of surgical intervention for pancreatic necrosis;
- Length of ICU and total hospital stay.

Results

- Study medication switched to open antibiotic treatment, due to clinical deterioration in 28% (antibiotic group) vs 46% (placebo group) ($p = 0.04$). (See Table 23.6.)

Table 23.6 Summary of results

| Primary endpoint | Antibiotics | Placebo | <i>p</i> |
|------------------------------------|-------------|------------|----------|
| Infected necrosis | 12% | 9% | ns |
| Secondary endpoints | | | |
| Mortality | 5% | 7% | ns |
| CSS, median points (range) | 1 (0–4) | 1 (0–4) | ns |
| Surgical intervention | 17% | 11% | ns |
| Hospital stay, median days (range) | 21 (7–237) | 18 (3–129) | ns |

Discussion

Although previous trials had reported conflicting results, surveys show that the majority of UK surgeons routinely use prophylactic antibiotics in the management of patients with predicted severe acute pancreatitis. This well-designed, double-blind, and placebo-controlled study did not detect any significant benefits, in terms of overall morbidity and mortality, the need for surgical intervention, ICU stay, and total hospital stay, in patients with predicted severe pancreatitis who received prophylactic ciprofloxacin and metronidazole, compared with those who did not. The authors concluded that antibiotics should be used ‘on demand’.

Problems

- Significantly higher proportion of placebo group patients required switch to non-study medication, due to clinical deterioration (46% vs 28%), suggesting that prophylactic antibiotics may have a protective effect against the development of systemic (extra-pancreatic) complications. Furthermore, the fact that antibiotics were started in nearly half of the placebo group after a median of 5d introduces bias against the treatment effect, making interpretation of the results more difficult.
- Some meta-analyses have shown marginal effects in favour of antibiotic prophylaxis. However, published trials show significant heterogeneity, in terms of the antibiotic regimens used, populations studied, and endpoints analysed, making the results of such meta-analyses less reliable.
- Recently published guidelines of the British Society of Gastroenterology conclude that there is insufficient evidence to make recommendations for or against the routine use of prophylactic antibiotics in patients with predicted severe acute pancreatitis.

Pancreatic cancer: adjuvant therapy

ESPAC-3 (European Study group for PAncreatic CAncer) trial: Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection, a randomized controlled trial.

AUTHORS: Neoptolemos J, Stocken D, Bassi C et al.

REFERENCE: JAMA (2010) 304, 1073–81.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Adjuvant chemotherapy after resection of pancreatic cancer improves overall survival. There is no survival advantage with gemcitabine over fluorouracil with folinic acid.

Impact

Chemotherapy, with either fluorouracil or gemcitabine post-pancreatic cancer resection, should remain routine practice.

Aims

Pancreatic cancer has a poor prognosis, with a 5y survival of <5%. Surgery can improve 5y survival rates to ~10%. There is a clear need to improve long-term outcome for this major cause of cancer death. The ESPAC-1 study showed no survival benefit for adjuvant chemoradiotherapy but revealed a potential benefit for adjuvant chemotherapy in patients with resected pancreatic cancer. Gemcitabine has been shown to be superior to fluorouracil in advanced pancreatic cancer. Therefore, the aim of ESPAC-3 was to determine whether fluorouracil or gemcitabine was superior in patients with resected pancreatic cancer.

Methods

Patients: 1,149 patients from 159 pancreatic cancer centres in Europe, Australasia, Japan, and Canada.

Inclusion criteria: Patients who had undergone complete macroscopic (R0 or R1) resection of ductal adenocarcinoma of the pancreas.

Exclusion criteria: Presence of malignant ascites, peritoneal metastases, or distal spread to abdominal or extra-abdominal organs and R2 resection.

Groups:

- Six cycles of folinic acid and fluorouracil ($n = 551$);
- Six cycles of gemcitabine ($n = 537$).

Primary endpoint: Overall survival.

Secondary endpoints: PFS, toxicity, and QoL.

Results

Final analysis performed on an ITT basis after median F/U of 34.2mo and 753 (69%) deaths.

- Median survival for those treated with folinic acid and fluorouracil was 23mo vs 23.6mo for those receiving gemcitabine ($p = 0.39$);
- Treatment-related adverse events were commoner in the fluorouracil/folinic acid group (14 vs 7.5%, $p \leq 0.001$);
- No difference between groups for PFS or QoL scores.

Discussion

The value of adjuvant chemotherapy post-pancreatic cancer resection is now established. This trial showed no advantage, in terms of overall survival, PFS, and QoL, with gemcitabine over fluorouracil. Stomatitis and diarrhoea were significantly commoner in the fluorouracil group, whereas haematological toxicity was significantly increased in the gemcitabine group. ESPAC-4 is designed to assess combination chemotherapy with gemcitabine plus capecitabine vs gemcitabine alone, and is currently recruiting.

Problems

- This was a large multicentre international trial involving 159 centres in 17 different countries. To recruit the numbers needed for this study to be appropriately powered, a large number of centres was necessary. This may lead to variability in both surgical technique/expertise and quality/methodology in pathological analysis, both of which may, in turn, influence long-term outcome.

Colorectal cancer: screening

Effect of faecal occult blood screening on mortality from colorectal cancer.

AUTHORS: Scholefield J, Moss S, Sufi F *et al.*

REFERENCE: *Gut* (2002) **50**, 840–4.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

UK-based RCT demonstrating a significant reduction in mortality from CRC in a large population that was offered screening by faecal occult blood (FOB) testing.

Impact

A national screening programme for CRC has commenced in the UK and will include all individuals aged 60–75y.

Aims

CRC is the second commonest cause of cancer deaths in the UK. This trial was designed to determine whether screening by FOB testing could reduce the mortality from CRC in the screened population vs controls. As concerns had been raised about possible adverse effects (such as colonoscopy-related complications and psychological harm) in the screened population, the authors also examined mortality from other causes in detail.

Methods

Patients: 152,850 patients living in the Nottingham area of the UK.

Inclusion criteria:

- Individuals aged 45–74y;
- No previous CRC or other serious illness within the last 5y.

Groups:

- FOB testing every 2y. Those with positive tests offered colonoscopy and then treated accordingly ($n = 76,466$);
- No intervention ($n = 76,384$).

Primary endpoint: CRC-related mortality.

Secondary endpoints:

- Incidence of CRC;
- All-cause mortality;
- Cause-specific mortality, with special reference to ischaemic heart disease and suicide.

Follow-up: Through local hospital records and flagging at the Office for National Statistics. Case notes reviewed for all certified and registered CRC cases. Median F/U 11.7y. ITT analysis.

Results

Table 23.7 Summary of results

| Primary endpoint | Intervention | No intervention | <i>p</i> |
|---------------------|--------------|-----------------|----------|
| CRC mortality | 0.7 | 0.8 | <0.01 |
| Secondary endpoints | | | |
| Incidence of CRC | 1.5 | 1.5 | 0.7 |
| All-cause mortality | 24.1 | 24.1 | 0.8 |
| IHD mortality | 5.9 | 5.9 | ns |
| Suicide | 0.07 | 0.07 | ns |

Values represent rates per 1,000 person-years. IHD, ischaemic heart disease.

Discussion

This large trial demonstrated a 13% reduction in mortality from CRC among individuals who were offered screening by FOB testing. A reduction of 27% was seen when only individuals who accepted the invitation for screening were included in the analysis. Furthermore, in contrast with some early reports, there was no evidence of increased mortality from ischaemic heart disease or suicide in the screened group. These results led to the now firmly established bowel cancer screening programme in the UK. (See Table 23.7.)

Problems

- Despite a compliance rate of 57%, a significant reduction in CRC mortality was seen in the screened population. It was speculated that compliance would increase with a national screening programme; however, analysis of the first 1 million screening tests performed in the programme¹ found a similar uptake of 52%.
- Colonoscopy is operator-dependent, and the potential for missed pathology (e.g. adenomas) exists. Quality assurance issues are therefore paramount with the setting up of a screening programme to ensure operators are of the highest standard, with minimal complication rates and consistently high adenoma detection rates.
- Colonoscopy is not without risk. Analysis of the first 2 million invited in the screening programme resulted in 17,192 undergoing colonoscopy. There were 42 cases of bleeding, 12 of whom required admission. A total of 17 perforations were recorded. No deaths occurred due to screening.¹

References

1. Logan RFA, Patnick J, Nickerson C, et al. (2012). Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut* 61, 1439–46.

Colorectal cancer: open vs laparoscopic surgery

CLASICC (Conventional vs Laparoscopic-Assisted Surgery In patients with Colorectal Cancer) trial follow up: Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer.

AUTHORS: Green BL, Marshall HC, Collinson F *et al.*

REFERENCE: *Br J Surg* (2013) **100**, 75–82.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The trial was the first major UK RCT of laparoscopic vs open surgery for colon and rectal cancer. It confirms the long-term results of both approaches are equivalent at 10y F/U.

Impact

Laparoscopic surgery should be the treatment of choice, enabling patients to benefit from earlier functional recovery, reduced length of stay, and decreased post-operative pain, with no detriment to long-term survival outcomes.

Aims

Earlier non-randomized studies had raised concerns about the oncological safety of laparoscopic resections in the management of patients with CRC. The CLASICC trial was designed to address these concerns and finished recruiting in 2002. Previous reports of this trial demonstrated improved short-term outcomes with laparoscopic surgery, in terms of reduced hospital stay, fewer wound complications, and expedited return to normal function. CLASICC 3y and 5y analyses showed comparable outcomes for overall survival and DFS. The trial was designed to assess long-term outcomes, with this paper reporting the 10y F/U.

Methods

Patients: 794 patients from 27 centres in the UK.

Inclusion criteria:

- Operable CRC (except for transverse colon malignancies);
- Suitable for right or left hemicolectomy, sigmoid colectomy, anterior resection, or abdominoperineal resection.

Exclusion criteria:

- Pregnancy or contraindications to pneumoperitoneum (chronic cardiac or pulmonary disease);
- Acute GI obstruction or GI disease requiring surgery;
- Synchronous adenocarcinomas or malignant disease in past 5y.

Groups:

- Laparoscopically assisted resection ($n = 526$);
- Conventional (open) resection ($n = 268$).

Long-term endpoints:

- Overall survival and DFS;
- Locoregional, distant and port site/wound recurrences.

Other endpoints (previously reported):

- Short-term endpoints reported in 2005 demonstrated no difference between laparoscopic vs open surgery, in terms of rate of positive resection margins, proportion of Dukes' C2 tumours, in-hospital mortality, complication rates (at 30d and 3mo), QoL measures up to 3mo after surgery, and transfusion requirement;
- *3y and 5y F/U* (published in 2007 and 2010, respectively) found no difference between the two groups for overall survival and DFS.

Results

- ITT analysis: No significant differences seen between the open and laparoscopic groups in relation to overall survival (78.3mo vs 82.7mo, $p = 0.78$) and DFS (89.5mo vs 77mo, $p = 0.589$);
- There was no difference between procedures for locoregional or distant recurrences;
- Resection margins: Among patients who underwent anterior resection, subgroup analysis revealed a 2-fold increase in the rate of positive resection margins in the laparoscopic group vs the open group (not statistically significant: 12% vs 6%, respectively; $p = 0.2$). This did not translate to any difference in overall survival or DFS at 10y F/U;
- 29% of laparoscopic group converted to open. Overall survival and DFS equivalent for converted rectal cases, but worse outcomes for colonic cancers.

Discussion

The results of this trial confirm that laparoscopic CRC surgery is equivalent to open surgery, with respect to long-term outcomes of overall survival and DFS. The laparoscopic approach offers short-term benefits over open surgery and equivalent long-term outcomes. Laparoscopic surgery should therefore be considered the approach of choice.

Problems

- High rate of conversion to open operation probably reflects the learning curve of this form of surgery during the trial period.
- Since 1996, there have been significant advances in staging (e.g. use of MRI) and neoadjuvant therapy.
- Although just under one-third were converted from laparoscopic to open, the overall analysis was performed on an ITT basis.

Colorectal cancer: anti-angiogenic treatment

Bevacizumab colon study: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer.

AUTHORS: Hurwitz H, Fehrenbacher L, Novotny W *et al.*

REFERENCE: *N Engl J Med* (2004) **350**, 2335–42.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This RCT confirms the benefit of an anti-angiogenic treatment (bevacizumab) in advanced CRC.

Impact

Tumour angiogenesis is established as a valid target for treatment of cancer. Bevacizumab can be clinically justified as an addition to standard drugs in patients with metastatic disease. However, it is an expensive addition that confronts publicly funded health systems with a challenge of affordability.

Aims

Angiogenesis is one of the six molecular 'hallmarks of cancer' identified in the late twentieth century. VEGF is one of its key biological regulators. Bevacizumab is a mouse-derived monoclonal antibody against VEGF. This trial aimed to determine whether bevacizumab could improve survival in metastatic CRC, when added to standard chemotherapy with irinotecan, bolus fluorouracil, and leucovorin (IFL).

Methods

Patients: 313 patients from 164 sites in the USA, Australia, and New Zealand.

Eligibility criteria:

- Histologically confirmed metastatic colorectal carcinoma;
- Bidimensionally measurable disease;
- Good performance status (ECOG 0 or 1);
- Life expectancy >3mo;
- No prior treatment for metastatic disease;
- Adequate organ function (kidney, liver, blood, heart, brain).

Groups: Bevacizumab could continue as maintenance after 96wk:

- IFL (once weekly for 4wk, cycle repeated every 6wk) and bevacizumab (every 2wk) ($n = 103$);
- IFL (once weekly for 4wk, cycle repeated every 6wk) and placebo (every 2wk) ($n = 100$);
- Fluorouracil, leucovorin (once weekly for 6wk, cycle repeated every 8wk), and bevacizumab (every 2wk) ($n = 110$).

Once safety of bevacizumab established, recruitment for this group stopped; results not reported.

Primary endpoint: Overall survival.

Secondary endpoints:

- PFS;
- Objective response: complete response (CR) and partial response (PR);
- Duration of response;
- Hospitalization.

Follow-up: Tumour assessment 6-weekly to 24wk, then 12-weekly until treatment end. All CR/PR subject to confirmatory assessment after 4wk.

Results

Table 23.8 Summary of results

| Primary endpoint | Placebo | Bevacizumab | HR | p |
|------------------------------|---------|-------------|------|--------|
| Median overall survival (mo) | 15.6 | 20.3 | 0.66 | <0.001 |
| Secondary endpoints | | | | |
| Median PFS (mo) | 6.2 | 10.6 | 0.54 | <0.001 |
| Objective response | 45% | 35% | — | 0.004 |
| Duration (mo) | 10.4 | 7.1 | 0.62 | 0.001 |
| Hospitalization | 39.6% | 44.9% | — | ns |

- There was a higher incidence of grades 3 and 4 adverse events with bevacizumab, mainly HTN, treatable with standard oral drugs. (See Table 23.8.)

Discussion

Anti-angiogenic treatment for cancer was first proposed by Folkman in 1971 (*J Exp Med* (1971) **133**, 275–88), but its development in the intervening three decades had been slow. This was the study that finally confirmed the paradigm. Bevacizumab was at least as effective as any other agent tested in phase 3 trials for CRC and was comparably tolerated to placebo.

Problems

- Challenges remain to understand the role of bevacizumab in combination therapy in advanced CRC, and both guidance and practice evolve and vary around the world. Another anti-EGFR monoclonal antibody cetuximab is also effective in enhancing PFS in KRAS ‘wild-type’ metastatic cancer.
- Access to bevacizumab is limited in publicly funded health systems on account of its high cost.
- There is research interest in markers of response to anti-angiogenic treatment. Several image-based markers of vascular function are being developed, including dynamic contrast MRI, positron emission tomography with oxygen-15 water, dynamic perfusion CT, and Doppler ultrasound.

Rectal cancer: total mesorectal excision

Mesorectal excision for rectal cancer.

AUTHORS: MacFarlane J, Ryall R, Heald R *et al.*

REFERENCE: *Lancet* (1993) **341**, 457–60.

STUDY DESIGN: Observational study.

EVIDENCE LEVEL: 3.

Key message

Meticulous surgical technique and surgical specialization can improve the outcome of patients with operable rectal cancer.

Impact

In the UK, total mesorectal excision (TME) is now the procedure of choice for resectable rectal cancer and is almost exclusively carried out by specialist colorectal surgeons.

Aims

Local recurrence is a serious problem in the management of rectal cancer, with an incidence ranging from 15% to 45% after conventional surgery. In an effort to determine the standards that would be acceptable for the surgical treatment of rectal cancer, the authors of this study reviewed the outcome of a large cohort of patients with resectable tumours who had been treated with TME alone (no adjuvant therapies).

Methods

Patients: Prospectively collected data from 281 consecutive TME resections for rectal cancer over a 13y period.

Protocol:

- Data retrospectively analysed by an independent assessor;
- Subset of 135 'high-risk' patients analysed separately, and comparisons made with the results of a contemporaneous North American trial that investigated the effect of adjuvant chemotherapy and chemoradiotherapy in the outcome of resectable rectal cancer;
- In accordance with the inclusion criteria, the 'high-risk' group only included patients with Dukes' B and C tumours, up to 12cm from the anal verge, who underwent macroscopically complete resection.

Endpoints:

- Local and overall recurrence rate;
- Disease-specific survival.

Follow-up: Every 3mo for the first 2y, every 6mo for the next 3y, and yearly thereafter. Median F/U 7.7y.

Results

- Recurrence rate:
 - 200 patients underwent anterior resections with curative intent;
 - Local recurrence rate (at 5y) 4%;
 - Overall recurrence rate (at 5y) 18%.
- High-risk group: Among the 135 'high-risk' patients:
 - Local recurrence rate (at 5y) 5% (95% CI 0–11%);
 - Overall recurrence rate (at 5y) 22%;
 - Disease-specific 5y survival 78% (95% CI 68–88%).
- Surgery and RT group:
 - Local recurrence rate (at 5y) 25%;
 - Overall recurrence rate (at 5y) 62.7%.
- Surgery and RT and chemotherapy group:
 - Local recurrence rate (at 5y) 13.5%;
 - Overall recurrence rate (at 5y) 41.5%.

Discussion

Local recurrence after surgical resection for rectal cancer causes disabling symptoms and is difficult to treat. These data suggested that TME could significantly reduce the incidence of local recurrence, perhaps improving overall survival. Interestingly, recurrence rates in this study following resection alone were much lower than those previously reported following conventional surgery combined with adjuvant chemotherapy and RT. Subsequent studies from other units have confirmed the superiority of TME to conventional surgery. The technique has been adopted by colorectal surgeons worldwide.

Problems

- This was an observational study, and therefore introduction of some bias is almost inevitable. However, the presented data were collected prospectively and analysed by an independent assessor, thus minimizing such bias as much as possible.
- The authors compared their results with those of a contemporaneous USA trial that greatly influenced the management of CRC at the time. Although the reported differences in recurrence rates were impressive, such comparisons between studies are unreliable, because they are based on diverse populations with distinct characteristics.
- Based on their excellent results, the authors questioned the need for adjuvant therapies after TME for rectal cancer. Subsequent studies have demonstrated that preoperative RT, combined with TME, reduces the risk of local recurrence even further, and adjuvant chemotherapy may improve overall survival in selected cases.

Rectal cancer: neoadjuvant radiotherapy

Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial.

AUTHORS: Sebag-Montefiore D, Stephens RJ, Steele R *et al.*

REFERENCE: *Lancet* (2009) **373**, 811–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Short-course preoperative RT significantly reduces the rate of local recurrence in resectable rectal cancer in patients undergoing TME.

Impact

Preoperative RT is recommended for the majority of patients with resectable rectal cancer.

Aims

Early reports of preoperative RT vs surgery alone demonstrated a reduction in local recurrence with RT. However, TME surgery was then shown to significantly reduce local recurrence, and the question subsequently arose as to whether preoperative RT was required when TME surgery was performed for rectal cancer. The CR07 trial was designed to compare preoperative RT followed by surgery vs surgery with selective post-operative chemotherapy for patients with an involved circumferential resection margin.

Methods

Patients: 1,350 patients with operable rectal cancer in 80 centres from four countries (UK, Canada, South Africa, New Zealand).

Inclusion criteria: Resectable rectal adenocarcinoma within 15cm from the anal verge, and no evidence of metastatic disease.

Groups:

- Short-course preoperative RT (SCPRT), consisting of 25Gy in five consecutive daily fractions, followed by surgery within 7d ($n = 674$);
- Surgery, followed by selective post-operative chemoradiotherapy in patients with involved circumferential resection margin, ($n = 676$). Therapy consisted of 45Gy in 25 fractions with concurrent 5-FU.

Primary endpoint: Local recurrence.

Secondary endpoints: Overall survival and DFS.

Follow up: 3-monthly for first year, then 6-monthly for second and third years, yearly thereafter.

Results

- A total of 99 local recurrences, 27 (4%) in the SCPRT group and 72 (11%) in the selective post-operative chemoradiotherapy group;
- 61% RRR for local recurrence in patients receiving SCPRT, and an absolute difference of 6% at 3y (4.4% SCPRT vs 10.6% selective post-operative chemoradiotherapy);
- No difference in overall survival between the two groups (5y survival of 70.3% SCPRT vs 67.9% selective group, $p = 0.4$); however, there was an absolute difference of 6% in DFS between the two groups at 3y post-operatively (77.5% vs 71.5%, $p = 0.013$).

Discussion

This trial, together with results from the Dutch trial (Kapiteijn E *et al.* *N Engl J Med* (2001) **345**, 638–46), provides very clear evidence that preoperative RT significantly reduces the rate of local recurrence in the era of TME surgery. There was no difference seen in the benefit of SCPRT, with respect to the height of the tumour from the anal verge and TNM stage.

Problems

- Although TME was not mandated within the trial design, surgeons considered it to be achieved in 93% of resections.
- Preoperative staging in this trial was not standardized. Current staging with MRI allows accurate assessment of both T and N stages of newly diagnosed rectal cancers. Patients with an involved circumferential resection margin can be identified; this therefore allows the appropriate decision of whether SCPRT followed by surgery or downsizing/staging with long-course chemoradiotherapy is the optimal management.
- Analysis of recurrence rates depending upon the level of tumour was a subgroup analysis and was not appropriately powered. However, this did show a reduced benefit from RT in the upper rectum. It has therefore been widely inferred that there may be a far weaker argument for giving preoperative RT to upper rectal cancers. It has to be emphasized that both this study and the Dutch study were not powered to address this question.

Rectal cancer: long-course chemoradiotherapy

Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results.

AUTHORS: Habr-Gama A, Perez R, Kiss D *et al.*

REFERENCE: *Ann Surg* (2004) **240**, 711–17.

STUDY DESIGN: Observational.

EVIDENCE LEVEL: 3.

Key message

Long-term outcome of stage 0 rectal cancer post-chemoradiotherapy is excellent, regardless of whether patients undergo surgery or observation only.

Impact

Intensive observation, following a complete clinical response to chemoradiotherapy, may be an acceptable treatment approach, with good long-term outcomes.

Aims

Neoadjuvant chemoradiotherapy treatment for rectal cancer leads to tumour downstaging in the majority of cases, and, in some cases, it may result in either a complete clinical response (absence of clinically detectable residual tumour) or a complete pathological response (absence of viable tumour cells after full pathological specimen examination). Surgical resection may be associated with significant morbidity, stoma formation, and mortality. In patients with a complete response, the benefits of surgery vs the associated risks are now being questioned. The aim of this study was to compare the long-term results of operative and non-operative treatments for patients with stage 0 rectal cancer.

Methods

Patients: 265 patients at a single centre.

Inclusion criteria:

- Adenocarcinoma of the distal rectum;
- Resectable lesion within 7cm of the anal verge.

Exclusion criteria: Presence of distant metastases.

Groups: 8wk post-completion of long-course chemoradiotherapy, patients underwent assessment using identical pretreatment clinical, endoscopic, and radiological parameters. The 265 patients were divided into two groups, based upon these findings:

- Incomplete clinical response was seen in 194 patients (73.2%). These patients underwent radical surgery and histological analysis. Stage 0 rectal cancer (pT0N0M0) was seen in 22 (8.3%) patients who formed the *resection group*;

- **Observation group** ($n = 71$, 26.8%) who had complete clinical response and underwent observation only.

Endpoints: Overall survival, DFS, and recurrence

Follow up:

- **Resection group:** Clinic visits 3-monthly for the first 2y, and then 6-monthly for subsequent years.;
- **Observation group:** Monthly clinical assessments, proctoscopy \pm biopsies and carcinoembryonic antigen (CEA) measurements. Abdominal and pelvic CT, and chest radiograph 6-monthly for the first-12mo. In y 2 and 3, patients underwent clinic visits every 2mo and 6mo, respectively.

Results

- No significant differences between the observation and resection groups in relation to patient demographics, tumour size, or T stage;
- Overall survival and DFS at 5y were 100% and 92% for the observation group, and 88% and 83% for the resection group ($p = 0.2$);
- Observation group: two patients developed endoluminal recurrence, (one treated by local excision, and the other with brachytherapy). Three patients (4.2%) developed systemic metastases treated with chemotherapy;
- Resection group: nine abdominoperineal resections and 13 sphincter-saving procedures. No surgical mortality, reoperation, or complications requiring ICU admission. Two parastomal hernias requiring surgery. Two patients died from unresectable metastatic disease, while one further patient was receiving chemotherapy for metastatic disease.

Discussion

A 'watch and wait' policy for stage 0 disease is associated with excellent long-term outcomes. However, the success of this policy will depend upon close clinical and radiological surveillance. Patients who undergo major surgery for stage 0 disease, with its associated morbidity and mortality risks, had no survival advantage in this study, compared to an observation strategy.

Problems

- Single-centre, non-randomized study involving small numbers (only 22 in resection group).
- No use of MRI to stage cancers pre- and post-treatment and in surveillance. This would provide information on both circumferential resection margin and nodal status, both of which are vital to guide treatment strategies.
- It is important that the definition of a complete clinical response is standardized.

Hernia repair: type of surgery

Laparoscopic versus open repair of groin hernia: a randomised comparison.

AUTHORS: The MRC Laparoscopic Groin Hernia Trial Group.

REFERENCE: *Lancet* (1999) **354**, 185–90.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First large UK trial to show significant advantages for patients who undergo laparoscopic repair of groin hernia, compared with those who have an open procedure.

Impact

Laparoscopic repair of groin hernia is increasingly gaining acceptance in the UK and is already the procedure of choice in many other countries. Laparoscopic surgery has now been approved in the UK as one of the treatment options for the repair of inguinal hernia.

Aims

UK surgeons have been slow to adopt laparoscopic repair of inguinal hernia, mainly because of early reports of rare serious complications. This trial was designed to compare laparoscopic with open repair of groin hernia, in order to evaluate its safety and to determine whether it was associated with any advantages for patients.

Methods

Patients: 928 patients from 26 hospitals in the UK and Ireland.

Inclusion criteria:

- 1° or recurrent femoral or inguinal hernia (unilateral or bilateral) that was not incarcerated and not inguinoscrotal;
- Fit for anaesthesia.

Exclusion criteria:

- Previous midline or paramedian incision;
- Uncorrected coagulation disorder;
- Pregnancy.

Groups:

- Laparoscopic repair: either transabdominal preperitoneal (TAPP) or totally extraperitoneal (TEP), according to surgeon preference ($n = 468$);
- Open repair ($n = 460$).

Principal outcome measures:

- Complications;
- Return to usual social activities;
- Groin pain persisting 1y post-operatively;
- Cost to health services.

Follow-up: Clinical review at 1wk, postal questionnaire at 3mo, questionnaire and clinical review at 1y.

Results

Table 23.9 Summary of results

| Measure | Laparoscopic (n = 468) | Open (n = 460) | p |
|---------------------------------|------------------------|----------------|--------|
| Intra-operative complications | | | |
| Major | 3 (0.6%) | 1 (0.2%) | ns |
| Overall | 25 (5.6%) | 6 (1.4%) | <0.001 |
| Post-operative complications | 108 (29.9%) | 155 (43.6%) | <0.001 |
| Return to social activities (d) | 10 (7–21) | 14 (7–28) | <0.01 |
| Pain in the groin at 1y | 113 (28.7%) | 133 (36.7%) | 0.02 |
| Recurrence at 1y | 7 (1.9%) | 0 | 0.02 |

- Laparoscopic repair costs (UK) £314 more than open repair. The difference decreased to £129, when 100% reusable equipment was used. (See Table 23.9.)

Discussion

Early non-randomized studies had raised concerns regarding the safety of laparoscopic repair of inguinal hernia. In this trial, although more serious complications occurred in the laparoscopic group (3 vs 1), the numbers were too small for meaningful analysis. Furthermore, this study demonstrated clear advantages associated with laparoscopic repair, in terms of wound-related complications, time for return to usual social activities, and persistent pain in the groin, following the procedure (all three patients who reported severe pain after 1y were in the open repair group).

Problems

- All three serious intraoperative complications in this trial occurred in the TAPP group. A recent meta-analysis confirmed a small, but statistically significant, difference between the two types of laparoscopic repair, in terms of major (visceral or vascular) complications. However, there is evidence that the incidence of these complications reduces with experience and is exceedingly low when the procedures (both TAPP and TEP) are performed by experienced surgeons.
- There was a higher incidence of recurrence in the laparoscopic vs the open group after 1y. However, subsequent trials and meta-analyses have not found significant differences between the two procedures.
- Little direct evidence to support one laparoscopic procedure (TAPP or TEP) over the other. One small RCT found none. The choice of procedure largely depends on the individual surgeon's experience.
- Laparoscopic hernia repair is more expensive than open repair, although the difference is significantly lower with reusable instruments.

Perioperative care: enhanced recovery

Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery.

AUTHORS: Vlug M, Wind J, Hollmann M *et al.*

REFERENCE: *Ann Surg* (2011) 254, 868–75.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

For patients undergoing colonic surgery, optimal perioperative treatment, in terms of shortest hospital stay, is laparoscopic resection embedded within a fast-track recovery programme.

Impact

Laparoscopic surgery within a fast-track recovery programme is now considered the management of choice.

Aims

Laparoscopic surgery and the use of enhanced recovery programmes, as first reported by Kehlet *et al.* (*Curr Opin Crit Care* (2009) 15, 355–8), have been two of the leading advances in the perioperative care of patients undergoing GI surgery. Enhanced recovery programmes incorporate a multimodal approach, aimed at reducing the surgical stress response, resulting in a faster return to normal function. Patients may undergo standard care or fast-track care with either an open or laparoscopic approach to surgery. The aim of this paper was to perform the first RCT to compare patients undergoing colonic surgery with these four possible combinations of care.

Methods

Patients: 427 patients at nine Dutch hospitals.

Inclusion criteria:

- Age between 40 and 80y;
- ASA grades 1–3;
- Elective segmental colectomy for histologically proven adenocarcinoma or adenoma;
- No evidence of metastatic disease.

Exclusion criteria:

- No availability of laparoscopic surgeon;
- Not emergency surgery;
- No previous midline laparotomy;
- No planned stoma.

Groups: 2 × 2 trial design:

- Laparoscopy/fast track ($n = 106$);
- Open surgery/fast track ($n = 103$);
- Laparoscopy/standard care: ($n = 110$);
- Open surgery/standard care: ($n = 108$).

Primary endpoint: Total hospital stay (THS) measured in days, defined as post-operative hospital stay (PHS) plus additional hospitalization, if patients were readmitted within 30d of surgery.

Secondary endpoints: PHS, overall morbidity, reoperation rate, readmission rate, in-hospital mortality, QoL at 2 and 4wk, patient satisfaction 4wk post-operatively and in-hospital costs.

Results

Table 23.10 Summary of results

| | Lap/FT | Open/FT | Lap/SD | Open/SD | |
|----------------------|---------|----------|-------------|----------|-------------|
| THS (d, median, IQR) | 5 (4–8) | 7 (5–11) | 6 (4.5–9.5) | 7 (6–13) | $p < 0.001$ |

FT, fast track; SD, standard care.

- Patients randomized to the laparoscopic/fast-track group had a significantly shorter hospital stay than the other three groups;
- Linear regression analysis identified laparoscopy as the only independent factor to influence the length of stay;
- No significant differences between the four treatment groups regarding overall, major, or minor morbidity; reoperation rate; readmission rate; in-hospital mortality; and QoL scores. (See Table 23.10.)

Discussion

This well-powered RCT showed laparoscopic surgery, combined with a fast-track recovery programme, to result in a significantly faster recovery from surgery than other treatment combinations. The goal of fast-track programmes is to accelerate patients' recovery, resulting in a reduced hospital stay.

Problems

- The blinding of treatment was limited, as the authors commented that the 'majority of patients could not resist looking under their abdominal dressings'. However, there was a clearly defined strict discharge criteria which had to be met, before discharge was allowed.
- The study was performed over a 4y period across nine centres. This may have led to variations in care over this time and possible adoption of fast-track elements into standard care.
- Six of the 15 fast-track items were included in 'standard care', as it was felt unethical to omit these modern advances in post-operative care.
- Nine centres were used; therefore, at least nine surgeons were involved, which would lead to surgical variability. The reoperation rate of 18% in the open/standard care group was higher than the Netherlands mean rate (11%) and a possible cause for concern, suggesting variability in the surgical technique.

Intensive care

Introduction 650

Catecholamines in septic shock 652

Evidence-based intervention to reduce catheter-related
bloodstream infections 654

Extracorporeal membrane oxygenation in adult respiratory
failure 656

Glycaemic control in critically ill patients 658

High-frequency oscillation for acute respiratory distress
syndrome 660

International guidelines for the management of severe
sepsis and septic shock 662

Proton pump inhibitors vs histamine (H₂) receptor
blockers 664

Sedation and ventilator weaning protocol 666

Steroids in septic shock 668

Therapeutic hypothermia 670

Introduction

In the last two decades, intensive care has come a very long way. The phenomenal developments clinically, academically, organizationally, and professionally during this relatively short space of time have all helped to define a specialty that has not only come of age but has established a distinct distance from its parent specialties. Intensive care in the UK now has an established Faculty and continues to forge ahead in expanding an independent research and evidence base.

The field is rapidly changing, with cutting-edge ideas driving clinical progress. Through the papers considered in this chapter, various innovations are described that have had a direct impact on everyday clinical practice. The evidence base is recognized to be fluid, not concrete. However, recognition of a shortfall in hard evidence continues to be a potent driver for testing existing concepts, though we accept that none of the trials described here is the 'last word'. Some of the trials we included failed to show any significant difference in outcome, which perhaps would support the above-mentioned view. There are also a couple of other trials that we were unable to include in the chapter that we would also recommend reading, including:

- A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* (1999) **340**, 409–17.
- Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* (2013) **368**, 2159–68.

Catecholamines in septic shock

VASST (Vasopressin And Septic Shock Trial): Vasopressin versus norepinephrine infusion in patients with septic shock.

AUTHORS: VASST Study Investigators.

REFERENCE: *N Engl J Med* (2008) **358**, 877–87.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The use of vasopressin did not result in a decrease in 28d mortality. Vasopressin was not associated with significant adverse effects. In the stratum of less severe septic shock, vasopressin was associated with less mortality than norepinephrine.

Impact

Vasopressin has been used as an adjunct in refractory septic shock, when high doses of norepinephrine are required to achieve target BP. This study showed that vasopressin on its own does not impact on mortality and is no better than norepinephrine.

Aims

Vasopressin is commonly used as an adjunct to catecholamines to support BP in refractory septic shock. However, its effect on mortality was not known. The authors aimed to determine whether vasopressin would reduce mortality in patients with septic shock being treated with conventional (catecholamine) vasopressors, compared with norepinephrine.

Methods

Patients: 778 patients across multiple centres.

Inclusion criteria: Patients with septic shock, receiving a minimum of 5 micrograms of norepinephrine per minute.

Groups: Assigned to receive (in addition to open-label vasopressors):

- Low-dose vasopressin (0.01–0.03U/min) group ($n = 396$);
- Norepinephrine (5–15 micrograms/min) group ($n = 382$).

Primary outcome: Mortality rate 28d after the start of infusions.

Results

Table 24.1 Summary of results

| | 28d mortality (%), $p = 0.26$ | 90d mortality (%), $p = 0.11$ | Adverse events (%), $p = 1.00$ |
|----------------------|----------------------------------|----------------------------------|-----------------------------------|
| Vasopressin group | 35.4 | 43.9 | 10.3 |
| Norepinephrine group | 39.3 | 49.6 | 10.5 |

Discussion

The use of low-dose vasopressin did not reduce mortality rates, when compared with norepinephrine, among patients with septic shock treated with catecholamine vasopressors. Low-dose vasopressin (0.01–0.04U/min) did help in reducing norepinephrine requirements to achieve target BP. (See Table 24.1.)

Evidence-based intervention to reduce catheter-related bloodstream infections

An intervention to decrease catheter-related bloodstream infections in the ICU.

AUTHORS: Pronovost P, Needham D, Berenholtz S *et al.*

REFERENCE: *N Engl J Med* (2006) **355**, 2725–32.

STUDY DESIGN: Collaborative cohort study

EVIDENCE LEVEL: 1b.

Key message

Catheter-related bloodstream infection (CRBSI) is not only expensive, but potentially fatal. This study showed that implementation of evidence-based interventions in managing central access catheters reduced the rate of CRBSI to zero. This has had a positive impact on safety, quality of care, and the bundle care approach in patient management.

Impact

Evidence-based intervention has led to significant reduction in CRBSI. This study played an important role in the development and implementation of central access care bundles in insertion and maintenance of catheters.

Aims

CRBSI is costly and can be fatal. In the USA, an estimated \$2.3 billion is spent on the consequences of an estimated 80,000 infections and up to 28,000 deaths per year associated with CRBSIs. The aim of this study was to gauge if evidence-based interventions could reduce the rate of CRBSI and hence improve the quality and safety of patient care in ICUs.

Methods

Patients: Patients at 103 ICUs in Michigan in the USA.

Method:

- Collaborative cohort study. Retrospective and prospective analysis;
- Multilevel Poisson regression modelling was used to compare infection rates.

Study intervention:

- ICUs asked to designate a physician and nurse as team leaders;
- Five evidence-based interventions were recommended: hand-washing, full barrier precautions during the insertion of lines, cleaning skin with chlorhexidine, avoiding femoral site if possible, and removing unwanted lines.

Outcome measures: Rates of infection before, during, and up to 18mo after study intervention. Rates of CRBSI per 1,000 catheter-days were measured at 3mo intervals.

Results

- A total of 375,757 catheter-days' worth of data collected over 1,981 ICU months.
- Median rate of CRBSI per 1000 catheter-days decreased from 2.7 infections at baseline to 0 at 3mo, after implementation of the study intervention ($p \leq 0.002$);
- Mean rate per 1,000 catheter-days decreased from 7.7 at baseline to 1.4 at 16–18mo of F/U ($p < 0.002$);
- Significant decrease in infection rates from baseline: incidence rate ratios decreased from 0.62 (95% CI 0.47–0.81) at 0–3mo to 0.34 (95% CI 0.23–0.50) at 16–18mo.

Discussion

The five evidence-based interventions reduced the CRBSI rate significantly (by up to 66%). This was sustained in the F/U and has led to a significant change in the way the central lines are now managed.

Problems

- Design unable to make a direct causal link between the intervention and the reduced infection rates.
- Potential under-reporting of baseline infection rates prior to implementing intervention.
- No data on organisms underlying CRBSIs.

Extracorporeal membrane oxygenation in adult respiratory failure

CESAR (Conventional ventilation versus Extracorporeal membrane oxygenation for Severe Addult Respiratory failure) trial: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial.

AUTHORS: The CESAR TRIAL collaboration group (Peek G, Muqford M, Tiruvoipati R et al.).

REFERENCE: *Lancet* (2009) 374, 1351–63.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The mortality rate remains high in severe adult respiratory failure, despite improvements in ventilation and the use of adjuncts. The influenza A (H1N1 subtype) pandemic demonstrated similar outcomes. Extracorporeal membrane oxygenation (ECMO) has emerged as a potential rescue therapy for severe refractory hypoxaemia in these patients. This is a specialized therapy available at selected centres only.

Impact

The CESAR trial has been a highly relevant RCT of respiratory venovenous (VV)-ECMO in patients with severe adult respiratory failure. It demonstrated improved survival without disability at 6mo in patients transferred to an ECMO centre. The subsequent Australian and New Zealand case series after the H1N1 influenza pandemic also showed improved survival in ECMO patients.

Aims

Severe adult respiratory failure is multifactorial and carries a high mortality, despite improvements in ventilation techniques and other treatments (such as prone positioning, steroids, and inhaled nitric oxide (NO)). The authors of this paper aimed to delineate the safety, efficacy, and cost-effectiveness of ECMO, compared with conventional ventilation.

Methods

Patients: 180 patients across multiple centres in the UK.

Inclusion criteria:

- Patients aged 18–65y;
- Murray score >3 or pH <7.20 ;
- Reversible cause of respiratory failure.

Exclusion criteria

- High ventilatory pressure (peak inspiratory pressure of $>30\text{cmH}_2\text{O}$);
- High FiO_2 requirement for $>7\text{d}$;
- Intracranial bleeding;
- Contraindication to heparinization;
- Contraindication to continuation of active treatment.

Groups

- Traditional ventilation group (ventilation according to local protocols) ($n = 90$);
- ECMO group ($n = 90$).

Primary outcome: Death or severe disability at 6mo after randomization or before hospital discharge.

Secondary outcomes: Data about resource use and economic outcome (QALY) were also collected.

Results

Table 24.2 Summary of results

| Primary outcome | ECMO group | Traditional ventilation group | <i>p</i> |
|------------------------------------|-------------|-------------------------------|----------|
| Survival without disability at 6mo | 63% (57/90) | 47% (41/87) | 0.03 |

Discussion

The trial recommended transfer of severe adult respiratory patients with a Murray score of >3 or pH of <7.20 on optimal conventional management without improvement to an ECMO centre. Because of both the CESAR Trial and the emergence of the H1N1 pandemic, respiratory ECMO services are now commissioned at five centres within the UK. A further RCT could be possible between these five ECMO centres comparing ECMO as rescue therapy against conventional ventilation. (See Table 24.2.)

Problems

Important questions have been raised about the study and feasibility of ECMO:

- A total of 22 out of 90 patients in the ECMO group improved on conventional ventilation, without going on ECMO.
- The protocols for conventional ventilation were not standardized and uniform at the local centres.

Glycaemic control in critically ill patients

NICE-SUGAR (Normoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) trial: Intensive versus conventional glucose control in critically ill patients.

AUTHORS: NICE-SUGAR Study Investigators. Finfer S, Chittock D, Su S *et al.*

REFERENCE: *N Engl J Med* (2009) **360**, 1283–97.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There are conflicting results from trials examining the effects of tighter glucose control, with hypoglycaemia remaining a major concern in this group. This trial compared the use of tighter glucose control with a more conventional regimen. The mortality was higher in the tighter glucose control group.

Impact

This trial showed that critically ill patients who had tighter glucose control of between 81 and 108mg/dL were at higher risk of hypoglycaemia. The mortality in this group was also higher. The more conventional regimen—which aimed to keep the glucose at <180mg/dL—was associated with lower mortality. Hence, the previously adopted practice of intensive glucose control has been abandoned, in favour of a more conventional approach, in critically ill patients.

Aims

Hyperglycaemia is common in critically ill patients, and severe hyperglycaemia is known to be associated with increased morbidity and mortality. The optimum glucose level to be maintained in critically ill patients is unclear. This is likely to be because of the risks of severe hypoglycaemia, ambiguity in previous trials, and difficulty in achieving normoglycaemia in critically ill patients. The NICE-SUGAR trial was therefore devised to test the hypothesis that intensive glucose control reduces 90d mortality in critically ill patients.

Methods

Patients: 6,104 patients across multiple centres in the USA.

Inclusion criteria:

- Adult patients within 24h after admission to an ICU;
- Expected to require treatment in the ICU on 3 or more consecutive days.

Groups

- Intensive glucose control: 81–108mg/dL (4.5–6mmol/L) ($n = 3,054$);
- Conventional glucose control: <180mg/dL (<10mmol/L) ($n = 3,050$).

Primary endpoint: All-cause mortality within 90d of randomization.

Results

- Data with regard to the primary outcome at d 90 were available for 3,010 and 3,012 patients, respectively;
- There was no significant difference between the two treatment groups in the median number of days in the ICU ($p = 0.84$) or hospital ($p = 0.86$), or the median number of days of mechanical ventilation ($p = 0.56$) or RRT ($p = 0.39$). (See Table 24.3.)

Table 24.3 Summary of results

| | Mortality (%) ($p = 0.02$) | Severe hypoglycaemia (%) ($p < 0.001$) |
|--------------|---------------------------------|---|
| Intensive | 829 (27.5) | 206 (6.8) |
| Conventional | 751 (24.9) | 15 (0.5) |

Discussion

Hyperglycaemia is common in acutely ill patients. While it is associated with increased morbidity and mortality in a variety of patient subgroups, trials examining the effects of tight glucose control had shown conflicting results. This large RCT showed that intensive glucose control was associated with a 2.6% higher mortality (NNH = 38) and a significantly higher incidence of severe hypoglycaemia (glucose < 2.2 mmol/L).

Problems

Note that the findings differ from those of a recent meta-analysis showing intensive glucose control to not significantly alter mortality in critically ill patients (Wiener R, Wiener D, Larson R (2008) *JAMA* 300, 933–44).

High-frequency oscillation for acute respiratory distress syndrome

OSCAR (OSCillation for Acute Respiratory Distress Syndrome) study: High-frequency oscillation for acute respiratory distress syndrome.

AUTHORS: Young D, Lamb S, Shah S *et al.*; for the OSCAR Study Group.

REFERENCE: *N Engl J Med* (2013) **368**, 806–13.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Patients with acute respiratory distress syndrome (ARDS) need mechanical ventilation to maintain oxygenation, but conventional ventilation is known to cause 2° lung damage. This multicentre RCT comparing high-frequency oscillation (HFO) ventilation to conventional treatment in moderate to severe ARDS was the second trial published within a week, showing no benefit to using HFO.

Impact

HFO has been considered an alternative method of ventilation in moderate to severe ARDS unresponsive to more conventional protective lung ventilation. It was thought to cause less volutrauma and barotrauma to the diseased lung. However, this trial and another similar trial (OSCILLATE) showed no mortality benefit to using HFO, and these results may well lead to a decrease in its use.

Aims

Patients with moderate to severe ARDS require invasive ventilation to maintain oxygenation. Even optimized protective lung ventilation is associated with trauma of the diseased lung and, in many cases, provides inadequate oxygenation and CO₂ clearance. HFO ventilation was first used in the 1970s to minimize the haemodynamic effects of ventilation. This trial aimed to compare HFO with conventional ventilation, in order to determine whether HFO reduced complications or showed any survival benefit.

Methods

Patients: 795 patients across 29 centres in the UK.

Inclusion criteria:

- Moderate to severe ARDS with ratio of partial pressure of O₂ to FiO₂ of ≤ 200 mmHg (26.7 kPa);
- Ventilated for 48h.

Groups

- Conventional ventilation ($n = 397$);
- HFO ventilation ($n = 398$).

Primary outcome: All-cause mortality at 30d after randomization.

Results

Table 24.4 Summary of results

| Primary outcome | Conventional group | HFO group | <i>p</i> |
|-----------------|--------------------|-----------------|----------|
| Mortality | 163/397 (41.1%) | 166/398 (41.7%) | 0.85 |

- No significant difference in mortality between the groups ($p = 0.85$, chi-square test). (see Table 24.4);
- No difference in the risk-adjusted mortality or ventilator-free days.

Discussion

The idea behind this trial was to offer an alternative ventilation strategy in ARDS with refractory hypoxaemia. The advantage of having extremely low tidal volumes to reduce 2° lung damage would seem logical and could provide a less invasive alternative to ECMO, deliverable locally. However, as no mortality benefit was shown either in this study or in a similar one (OSCILLATE—*N Engl J Med* (2013) **368**, 795–805), published at the same time, there is now a question mark over the use of this treatment. Even those ICU clinicians who have supported its use in the past are no longer advocating the widespread continuation of this method of ventilation. The OSCILLATE study showed 47% mortality in the HFO ventilation group vs 35% in the control group (RR of death with HFO ventilation was 1.33, 95% CI 1.09–1.64, $p = 0.005$).

International guidelines for the management of severe sepsis and septic shock

Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012.

AUTHORS: Dellinger P, Levy M, Rhodes A *et al.*

REFERENCE: *Crit Care Med* (2013) **41**, 580–631.

STUDY DESIGN: International expert committee review/guidelines.

EVIDENCE LEVEL: 5.

Key message

This exercise aimed to provide an update to the surviving sepsis guidelines published in 2008. Key recommendations were listed in categories, including resuscitation, antimicrobial therapy, ventilation, and those specific for paediatric sepsis.

Impact

As with the previous guidelines, the objective was to provide a consistent practice across the globe. They have been largely successful in achieving that goal. However, there have been questions raised by some experts on some recommendations, based on what is perceived to be as inconsistent evidence.

Aims

Sepsis is a systemic, deleterious host response to infection, leading to severe sepsis (acute organ dysfunction 2° to documented or suspected infection) and septic shock (severe sepsis plus hypotension not reversible with fluid resuscitation). These are major health problems with high mortality. This consensus paper aimed to provide an update to the *Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock*, last published in 2008.

Design

The consensus committee consisted of 68 international experts, representing 30 organizations. The entire guidelines process was conducted, independent of any industry funding, and a formal conflict of interest policy was enforced throughout. A stand-alone meeting was held for all subgroup heads, co- and vice-chairs, and selected individuals. Teleconferences and electronic-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods

The principles of Grading of the Recommendations Assessment, Development, and Evaluation (GRADE) system was used to assess the quality of evidence from high (A) to very low (D). The strength of recommendation was strong (1) or weak (2). Some recommendations were ungraded (UG). The recommendations were put in three groups: (1) those directly targeting severe sepsis, (2) those targeting general care in critical illness, but considered high priority in sepsis, and (3) paediatric considerations.

Recommendations

Surviving sepsis campaign bundles

To be completed within 3 hours:

- Measure lactate level;
- Obtain blood cultures prior to the administration of antibiotics;
- Administer broad-spectrum antibiotics;
- Administer 30mL/kg of crystalloid for hypotension or lactate >4mmol/L.

To be completed within 6 hours:

- Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain an MAP of >65mmHg;
- In the event of persistent arterial hypotension, despite volume resuscitation (septic shock), or initial lactate 4mmol/L or more (36mg/dL):
 - Measure CVP;*
 - Measure ScvO₂*
- Re-measure lactate, if initial lactate was elevated.*

The details of recommendations can be referred in the original paper.

* Targets for quantitative resuscitation included in the guidelines are CVP of 8mmHg, SCVO₂ of 70%, and normalization of lactate.

Discussion

Strong agreement existed among a large cohort of international experts regarding many level 1 recommendations for the best care of patients with severe sepsis. Although a significant number of aspects of care have relatively weak support, evidence-based recommendations regarding the acute management of sepsis and septic shock are the foundation of improved outcomes for this important group of critically ill patients.

Proton pump inhibitors vs histamine (H₂) receptor blockers

Proton pump inhibitors versus histamine 2 receptor antagonists for stress ulcer prophylaxis in critically ill patients: a systematic review and meta-analysis.

AUTHORS: Alhazzani W, Alenezi F, Jaeschke R et al.

REFERENCE: *Crit Care Med* (2013) **41**, 693–705.

STUDY DESIGN: Systematic review and meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

This systematic review suggests PPIs are better in preventing clinically important upper GI bleeding, compared to H₂ blockers. However, there is no change in the secondary outcomes (discussed later) in either group.

Impact

There is no clear evidence from this review to suggest change in practice. The default standard is to use H₂ blockers and PPI in a select group of patients, i.e. those with a previous history of GI bleed, pre-admission use of PPI, extracorporeal circuits, and anticoagulation.

Aims

Bleeding from stress ulceration is an important cause of morbidity and mortality in critically ill patients. Histamine receptor (H₂) blockers and PPIs have been used for acid suppression to reduce the risk of bleeding from stress ulcer. This study aimed to determine the efficacy and safety of PPI vs H₂ receptor blockers in preventing upper GI bleeds in critically ill patients.

Methods

Search methodology:

- Search was made on Cochrane Central Registry of Controlled Trials, MEDLINE, EMBASE, ACPJC, CINHALL, online trial registry, conference database, and relevant reference articles;
- Randomized controlled, parallel-group trials comparing PPI vs H₂ blockers published before March 2012 were included;
- Fourteen trials enrolling 1,720 patients were included in the final analysis.

Primary outcomes: Clinically important upper GI bleeding and overt GI bleeding.

Secondary outcomes: Nosocomial pneumonia, ICU length of stay, ICU mortality, incidence of *Clostridium difficile* infection.

Results

- PPIs were more effective than H2 antagonists at reducing clinically important upper GI bleeding (RR 0.36; 95% CI 0.19–0.68; $p = 0.002$; $I = 0\%$) and overt upper GI bleeding (RR 0.35; 95% CI 0.21–0.59; $p < 0.0001$; $I = 15\%$);
- No difference between PPIs and H2 blockers in the risk of nosocomial pneumonia (RR 1.06; 95% CI 0.73–1.52; $p = 0.76$; $I = 0\%$), ICU mortality (RR 1.01; 95% CI 0.83–1.24; $p = 0.91$; $I = 0\%$), or ICU length of stay (mean difference -0.54 d; 95% CI -2.20 to 1.13 ; $p = 0.53$; $I = 39\%$);
- No trials reported on *C. difficile* infection.

Discussion

PPIs were found to be better at reducing clinically significant upper GI bleeding in critically ill patients. However, there was no difference in the secondary outcomes. The authors of this analysis did question the findings, due to sparse data and poor methodology among the trials, as well as the possibility of publication bias.

Sedation and ventilator weaning protocol

Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial.

AUTHORS: Girard T, Kress J, Fuchs B *et al.*

REFERENCE: *Lancet* (2008) **371**, 126–34.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

The approach to weaning sedation and mechanical ventilation has varied widely, and this trial helped to standardize these processes in critically ill patients. The trial results showed a more favourable outcome (i.e. a reduction in length of stay in both the ICU and hospital in patients who had a daily sedation hold).

Impact

This trial has led to a more organized approach towards weaning in ICU. Ventilator care bundles have been adopted across the board and have led to protocol-based weaning of sedation and ventilation. It is now standard practice to ask, at least daily, about the sedation score for each patient and, unless contraindicated, conduct a sedation hold. This approach has been broadly accepted as a step forward in decreasing the length of stay in the ICU.

Aims

Approaches to removal of sedation and mechanical ventilation for critically ill patients vary widely. This study aimed to assess a protocol that paired spontaneous awakening trials (SATs), i.e. daily interruption of sedatives, with spontaneous breathing trials (SBTs).

Methods

Patients: 336 mechanically ventilated patients in ICUs at four tertiary care hospitals in the USA.

Groups:

- Study group (daily SAT, followed by an SBT) ($n = 168$);
- Control group (sedation, usual care, plus daily SBT) ($n = 168$).

Primary endpoint: Time breathing without assistance.

Results

Table 24.5 Summary of results

| | Breathing without assistance (d) ($p = 0.02$) | Length of stay in ICU (d) ($p = 0.01$) | Length of stay in hospital (d) ($p = 0.04$) | Reintubation rates (%) ($p = 0.73$) |
|---------------|--|---|--|--|
| Study group | 14.7 | 9.1 | 14.9 | 13.8 |
| Control group | 11.6 | 12.9 | 19.2 | 12.5 |

- The results showed that patients in the study group were less likely to die (HR 0.68, 95% CI 0.50–0.92; $p = 0.01$) than the control group;
- For every seven patients treated with the intervention, one life was saved (NNT = 7.4, 95% CI 4.2–35.5). (See Table 24.5.)

Discussion

Interruption of sedatives daily with SBTs results in better outcomes in mechanically ventilated patients. This has become routine practice now, with a more standardized protocol.

Steroids in septic shock

CORTICUS study: Hydrocortisone therapy for patients with septic shock.

AUTHORS: Sprung C, Annane D, Key D *et al.*; for the CORTICUS Study Group.

REFERENCE: *N Engl J Med* (2008) **358**, 111–24.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In septic shock, cytokines suppress the cortisol response to adrenocorticotrophic hormone, and this can cause poor adrenal activity. This study showed that the use of hydrocortisone did not improve survival in septic shock, either overall or in patients who did not respond to corticotrophin. However, it did hasten the reversal of shock in patients in whom this was reversible.

Impact

This paper showed no significant effect of corticosteroid treatment on 28d mortality, intensive care, or hospital mortality. However, a GRADE 2B recommendation can be made for the use of low-dose corticosteroid in patients with vasopressor-dependent septic shock.

Aims

The incidence of septic shock in industrialized countries ranges from 50–100 per 100,000 population, with short term mortality of 20–50%. Septic shock is complicated by poor adrenal activity and resistance to corticosteroids through either fewer receptors or receptors with low affinity.

Hydrocortisone is widely used in patients with septic shock. In this multicentre, randomized, double-blind, placebo-controlled trial, patients were assigned to receive 6-hourly 50mg hydrocortisone for 5d or placebo. The aim was to clarify whether hydrocortisone therapy improved 28d mortality.

Methods

Patients: 499 patients across 52 centres in Israel.

Inclusion criteria:

- Clinical evidence of infection and systemic response to infection;
- Onset of shock within previous 72h;
- Hypoperfusion and organ dysfunction attributable to sepsis.

Exclusion criteria:

- Underlying disease with poor prognosis and life expectancy of <24h;
- Immunosuppression, and treatment with long-term corticosteroid within last 6mo or short-term within last 4wk.

Groups:

- Hydrocortisone group ($n = 251$);
- Placebo group ($n = 248$).

Primary endpoint: 28d mortality in patients who did not respond to the corticotrophin test.

Results

- Of the 499 patients in the study, 233 (46.7%) did not have a response to corticotrophin test (125 in the hydrocortisone group and 108 in the placebo group);
- At 28d, there was no significant difference in mortality between patients in the two study groups who did not have a response to corticotrophin (39.2% in the hydrocortisone group and 36.1% in the placebo group, $p = 0.69$) or between those who had a response to corticotrophin (28.8% in the hydrocortisone group and 28.7% in the placebo group, $p = 1.00$). At 28d, 86 of 251 patients in the hydrocortisone group (34.3%) and 78 of 248 patients in the placebo group (31.5%) had died ($p = 0.51$);
- In the hydrocortisone group, shock was reversed more quickly than in the placebo group. However, there were more episodes of superinfection, including new sepsis and septic shock.

Discussion

Hydrocortisone did not improve survival or reversal of shock in patients with septic shock, either overall or in patients without a response to corticotrophin. However, hydrocortisone did hasten the reversal of shock in patients in whom shock was reversed. Another large study (Annane D *et al.* (2002) *JAMA* **288**, 862–71) on steroid use in septic shock came to very different conclusions, showing that a 7d treatment of low-dose hydrocortisone and fludrocortisone significantly reduced the risk of death in patients with septic shock and relative adrenal insufficiency ($p = 0.02$). This indicates that the controversy has not yet been resolved. However, it would appear that there is role for low-dose hydrocortisone in patients with refractory septic shock unresponsive to fluids and vasopressors. New studies looking into mortality, timing, tapering, and adverse events associated with low-dose steroid in septic shock are required.

Therapeutic hypothermia

Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest.

AUTHORS: Hypothermia After Cardiac Arrest Study Group.

REFERENCE: *N Engl J Med* (2002) **346**, 549–56.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In patients successfully resuscitated after cardiac arrest due to VF, therapeutic mild hypothermia leads to better neurological recovery and reduced mortality.

Impact

Cardiac arrest is associated with widespread cerebral ischaemia and frequently leads to significant neurological impairment. Mild therapeutic hypothermia improves the neurological outcome after cardiac arrest due to VF, and, as a result, this practice has become widely adopted.

Aims

Widespread cerebral ischaemia after successful resuscitation from cardiac arrest leads to significant neurological impairment. This trial looked at the effect of mild therapeutic hypothermia on neurological recovery after cardiac arrest due to VF and aimed to determine whether this increased the rate of recovery.

Methods

Patients: 275 patients across multiple centres.

Groups:

- Hypothermia group ($n = 137$): Target temperature 32–34°C (measured in the bladder) over a period of 24h;
- Normothermia group ($n = 138$): Standard treatment with normothermia.

Inclusion criteria:

- Age 18–75y;
- Witnessed cardiac arrest;
- VF or non-perfusing VT as the initial cardiac rhythm;
- Presumed cause of arrest of cardiac origin;
- Estimated interval of 5–15min from patient's collapse to first attempt at resuscitation by emergency personnel;
- <60min from collapse to return of spontaneous circulation (ROSC).

Exclusion criteria:

- Tympanic membrane temperature <30°C on admission;
- Comatose state before cardiac arrest due to the administration of drugs depressing the CNS;

- Pregnancy;
- Response to verbal commands after ROSC and before randomization;
- Evidence of hypotension (MAP <60mmHg) >30min after ROSC and before randomization;
- Evidence of hypoxaemia (SpO_2 <85%) >15min after ROSC and before randomization;
- Terminal illness preceding arrest;
- Factors making participation in F/U unlikely;
- Enrolment in another study;
- Cardiac arrest after arrival of emergency medical personnel;
- Known pre-existing coagulopathy.

Primary outcome: Favourable neurological outcome within 6mo, defined as a Pittsburgh cerebral performance category of 1 (good recovery) or 2 (moderate disability) on a five-category scale; the other categories were 3 (severe disability), 4 (a vegetative state), and 5 (death).

Secondary outcomes:

- Overall mortality at 6mo;
- Rate of complications during the first 7d after cardiac arrest.

Results

Table 24.6 Summary of results

| | Favourable neurological outcome (%) | Mortality at 6mo (%) |
|--------------------|-------------------------------------|----------------------|
| Hypothermia group | 75 (55) | 56 (41) |
| Normothermia group | 54 (39) | 76 (55) |

- Favourable neurological outcome: RR 1.40, 95% CI 1.08–1.81;
- Mortality at 6mo: RR 0.74, 95% CI 0.58–0.95 (see Table 24.6).

Discussion

Mild therapeutic hypothermia leads to favourable neurological outcome, after successful resuscitation from cardiac arrest. This trial led to a widespread change in practice and the adoption of therapeutic hypothermia. The results have been extrapolated to all causes of cardiac arrests (in-hospital, out-of-hospital, and, to a certain extent, any rhythm). There are currently several ongoing studies that are looking to clarify whether it is hypothermia or maintaining normothermia that leads to the beneficial outcome.

Neurosurgery

- Introduction 674
- Corticosteroids in head injury 676
- Prophylactic phenytoin in head trauma 678
- Early surgery for intracerebral haemorrhage 680
- Nimodipine in subarachnoid haemorrhage 682
- Coiling or clipping for ruptured intracranial aneurysms 684
- Extracranial–intracranial bypass surgery for stroke prevention 686
- Decompressive surgery for spinal metastases 688
- Radiosurgery and brain metastases 690
- Adjuvant temozolomide for grade 4 astrocytoma 692
- Treatment of low-grade gliomas 694
- Surgery for lower back pain 696
- Instrumentation for spondylolisthesis 698
- Surgery for lumbar disc herniation 700
- Surgery for Parkinson's disease 702
- Surgery for temporal lobe epilepsy 704

Introduction

The Edwin Smith papyrus is a transcription of several ancient Egyptian documents dating back to the seventeenth century BC. It contains the world's first descriptions of neuroanatomy and details the diagnosis and management of head and spinal trauma, which remain accurate to this day. Since these ancient times, not until the turn of the twentieth century—heralded by the discovery of antiseptics by Lister and the development of anaesthesia—was the field of neurosurgery really born.

Initially, it was the general surgeons who undertook neurosurgery. Based on the studies of mapping neurological function to the brain by Hughlings Jackson and David Ferrier, Sir Rickman Godlee (1849–1925), nephew of Joseph Lister, and Sir William MacEwen (1848–1924), a Scotsman, were the first surgeons who were able to locate an intracranial tumour by clinical examination and thereby able to resect it. The work of these pioneers opened the door to specialist neurosurgeons.

Sir Victor Horsley (1857–1916), godson to Queen Victoria and son of the man who invented the Christmas card, was the world's first appointed specialist neurosurgeon. Working from the then known National Hospital for the Paralysed and Epileptics, he pioneered a series of firsts: laminectomy for spinal neoplasm, carotid ligation for cerebral aneurysm, curved skin flap, transcranial approach to the pituitary gland, intradural division of the trigeminal nerve root for trigeminal neuralgia, and surface marking of the cerebral cortex. With wide-ranging ability, Horsley also influenced other fields of medicine, one example being his study of the innervation of the larynx with Sir Felix Semons, resulting in the law that now defines the movement of the larynx.

Harvey Cushing (1869–1939) was educated at Yale, then Harvard Medical School, and worked in a number of prestigious institutions, including Johns Hopkins where he met his mentors Halsted and Osler. The first to extensively attempt the trans-sphenoid approach to the pituitary, his tireless study of his pituitary patients led to his descriptions of 'Cushing's disease' and 'Cushing's syndrome.' Furthermore, he pioneered surgery of skull base lesions and meningiomas. Among his many important scientific contributions is his discovery of the 'Cushing's response' and the development of the anaesthetic chart, which he devised while an intern anaesthetizing patients at Massachusetts General Hospital.

Since the time of these innovators, neurosurgery has developed at a rapid pace, alongside technological advances such as CT, MRI, stereotaxis, microscope, and neuroendoscopy. We look forward to an exciting century of development, as neurosurgery continues to demand more from technology, and now biotechnology, and these disciplines rise to meet that challenge.

Corticosteroids in head injury

The CRASH (**C**orticosteroid **R**andomization after **S**ignificant **H**ead **i**njury) trial is a randomized, multicentre, controlled trial to establish the effect of corticosteroids in head injury.

AUTHORS: CRASH trial collaborators.

REFERENCE: *Lancet* (2004) **364**, 1321–8; *Lancet* (2005) **365**, 1957–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the first randomized trial demonstrating an increased risk of death with corticosteroids following head injury.

Impact

Prior to CRASH, corticosteroids were often used in the treatment of head injury. In light of CRASH, this practice has been abandoned.

Aims

Corticosteroids were a common drug treatment for head injury; this practice was supported by a systematic review in 1997, which suggested that corticosteroids reduced the risk of death from head injury by 1–2%. CRASH, a multicentre international RCT, aims to confirm or refute these findings.

Methods

Patients: 10,008 (239 hospitals in 49 countries).

Inclusion criteria:

- Aged 16y or older;
- Head injury with GCS of 14 or less;
- Presented within 8h of injury;
- Uncertainty principle: If the treating clinician was uncertain whether or not to treat with corticosteroids.

Groups:

- Methylprednisolone, given as a 48h infusion ($n = 5,007$);
- Placebo ($n = 5,001$).

Follow-up: at 2wk and 6mo following head injury.

Primary endpoint:

- Death from any cause within 2wk of injury;
- Death and disability at 6mo.

Subgroup analysis: Effect of:

- Severity of injury;
- Time since injury;
- Presence or absence of major extracranial injury.

Results

Subgroup analysis yielded no increase in the relative risk of death at either 2wk or 6mo when patients were stratified according to severity of injury, time of injury, or the presence or absence of major extracranial injury. (See Table 25.1.)

Table 25.1 Summary of result

| Primary endpoint | Methylprednisolone | Placebo | <i>p</i> |
|-----------------------------------|--------------------|---------|----------|
| Death within 2wk of injury | 21% | 18% | 0.0001 |
| Death within 6mo of injury | 25.7% | 22.3% | 0.0001 |
| Death or severe disability at 6mo | 38.1% | 36.3% | 0.079 |

Discussion

Results from this trial demonstrate that not only do corticosteroids not reduce mortality following head injury at both 2wk and 6mo, they also seem to be associated with an increased risk in mortality. For this reason, the results obtained after 2wk F/U were reported early, leaving 6mo data to be reported later. This trial refutes any previous evidence supporting the routine use of corticosteroids in the management of head injury. Interestingly, two randomized trials have assessed the use of methylprednisolone in acute spinal cord injury (National Acute Spinal Cord Injury Studies, NASCIS, II and III2). NASCIS II results, released in the media before scientific publication, indicate that corticosteroids confer a benefit to neurologic recovery over placebo. However, the subsequent report reveals that this is not the case—an advantage was only seen in a post hoc analysis of a small subgroup ($n = 129$) who were treated <8 h after injury. Unfortunately, the placebo group treated <8 h after injury also did worse than the placebo group that was treated >8 h after injury, revealing further weaknesses in the study. Despite the criticisms of NASCIS II, NASCIS III sought to investigate the best corticosteroid dosing. Nearly 50% of the subjects had little or no motor deficits, and most of these were randomized to the lower-dose treatment group, making results difficult to interpret and to extrapolate to those with more significant deficits. These are only but a few of the criticisms of the NASCIS studies. CRASH, a more recent and thoughtful study, does remind us of the hazards of steroid use in acute trauma.

Problems

- The trial was designed to detect a survival difference of 2%. It may be criticized that this percentage is too small to be of clinical significance. However, taking into account the prevalence of head injury of 30 million worldwide, a 2% improvement in mortality would result in the saving of 600,000 lives.
- Head-injured patients receive numerous concomitant treatments, according to the unit protocol and to any extracranial injuries or complications. Concomitant therapies were not recorded. However, the data obtained above are to a high level of precision and are unlikely to be false negatives.

Prophylactic phenytoin in head trauma

A randomized, double-blind, controlled trial assessing the effect of phenytoin in preventing seizures following head trauma.

AUTHORS: Temkin NR, Dikmen SS, Wilensky AJ *et al.*

REFERENCE: *N Engl J Med* (1990) **323**, 497–502.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Phenytoin only provides effective seizure prophylaxis in the short term following severe head injury.

Impact

Phenytoin may be considered for seizure prophylaxis following severe head injury, but, also considering the need for therapeutic monitoring and idiosyncratic reactions, if started, its use should be limited to 1wk.

Aims

Seizures are a relatively common complication of severe head injury and can be extremely debilitating. Phenytoin had therefore been used for many years as prevention. However, clinical data were inconclusive, limited by subtherapeutic levels of the drug and statistical power. This study aims to assess in a randomized, double-blind, and controlled fashion whether prophylactic phenytoin reduces the incidence of seizures following severe head trauma.

Methods

Patients: 404 (one centre in the USA).

Inclusion criteria:

- Age ≥ 16 ;
- Either cortical contusion, depressed skull fracture, penetrating head wound, subdural, epidural, or intracerebral haematoma;
- Seizure within 24h of injury;
- GCS ≤ 10 .

Groups:

- Phenytoin ($n = 208$);
- Placebo ($n = 196$, 15 patients crossed over).

Follow-up: over 2y.

Primary endpoint: occurrence of seizures (early, occurring from time of drug loading to d 7; or late, occurring on d 8 or later).

Secondary endpoints:

- Adverse effects.

Results

Table 25.2 Summary of result

| Primary endpoint | Phenytoin | Placebo | <i>p</i> |
|------------------------------------|-----------|---------|----------|
| Occurrence of early seizures | 3.6% | 14.3% | 0.001 |
| Occurrence of late seizures | 27.5% | 21.1% | >0.2 |
| Secondary endpoints | | | |
| Rash causing stopping of treatment | 17 | 4 | <0.01 |
| Other drug reactions | 12 | 8 | |

- Mortality rates of both treatment groups were similar. (See Table 25.2.)

Discussion

This trial provides robust evidence that phenytoin prevents seizures up to 1wk following a severe head injury, but this benefit is no longer seen thereafter. Admirably, the maintenance of therapeutic drug levels in this study, compared to those before, was achieved.

Problems

- Cross-over of patients from the placebo group to the phenytoin group and stopping of treatment due to idiosyncratic reactions in this ITT analysis may have obscured results. However, 2° analysis considering these factors did not reveal a different result.
- With a negative result, there is some concern as to whether the study had sufficient power to detect a beneficial effect. However, statistical analysis revealed that it should.

Early surgery for intracerebral haemorrhage

STICH (International Surgical Trial in IntraCerebral Haemorrhage): Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas.

AUTHORS: Mendelow AD, Gregson BA, Fernandes HM et al.

REFERENCE: *Lancet* (2005) **365**, 387–97.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Early neurosurgical intervention confers no prognostic or survival benefit to patients with spontaneous supratentorial intracerebral haemorrhage (SSIH).

Impact

In patients presenting with SSIH but who have no clear indication for immediate surgery, it would be reasonable to consider a period of conservative treatment first and only proceed to surgery, if clinical indication arises.

Aims

Decompressing an intracerebral haematoma, thereby reducing intracranial pressure and increasing cerebral perfusion to the penumbra around the haematoma, should improve outcome. However, early clinical trials produced conflicting results. This RCT attempts to definitively establish whether early surgery has a role in treating those with SSIH.

Methods

Patients: 1,033 (83 centres in 27 countries).

Inclusion criteria:

- CT evidence of SSIH, with a minimum haematoma diameter of 2cm;
- Haemorrhage within 72h;
- GCS of ≥ 5 ;
- No structural cause of haemorrhage, e.g. aneurysms, arteriovenous malformation, tumour, trauma;
- Uncertainty regarding benefits of surgery or conservative management.

Groups:

- Surgery, within 24h of randomization ($n = 496$ patients assessed, 6% of whom surgery was delayed);
- Conservative management ($n = 529$ patients assessed, 26% crossed over).

Follow-up: 6mo.

Primary endpoint: Extended Glasgow Outcome Scale (GOS).

Secondary endpoints:

- Mortality;
- Barthel Index;
- Modified Rankin scale.

Results**Table 25.3** Summary of result

| Primary endpoint | Early surgery | Initial conservative therapy | <i>p</i> |
|--------------------------------------|---------------|------------------------------|----------|
| Favourable | 26% | 24% | 0.414 |
| Secondary endpoints | | | |
| Mortality | 36.3% | 37.4% | 0.678 |
| Favourable outcome: Barthel Index | 27% | 23% | 0.144 |
| Favourable outcome: Rankin scale | 33% | 28% | 0.116 |

- Subgroup analysis revealed a statistically significant favourable outcome from early surgery, if the depth of the haematoma was 1cm or less from the cortical surface ($p = 0.02$). (See Table 25.3.)

Discussion

Early surgery was not shown to confer any prognostic or survival benefits, compared with initial conservative management, in those with SSIH. However, in a prespecified subgroup of those with a haematoma of 1cm or less, early surgery may have been beneficial. Based on these findings, STICH II3, a randomized, multicentre worldwide trial comparing the effects of early surgery and initial conservative management on conscious patients with spontaneous lobar intracerebral haemorrhage of ≤ 1 cm from the cortical surface, was conceived—endpoints were similar to the original STICH trial. Results, just published in May 2013, failed to demonstrate an advantage with early surgery (favourable primary outcome of 41% and 38%, $p = 0.367$; and mortality of 18% and 24%, $p = 0.095$, with early surgery and initial conservative management, respectively). Limited by a 21% cross-over of the initial conservative management group to surgery, post hoc analysis suggested that those in the poor prognosis group were more likely to have a favourable outcome with early surgery ($p = 0.02$).

Problems

- Subgroup analysis requires cautious interpretation; though prespecified, this analysis requires a higher level of significance to be reached, in which case the results from this subgroup analysis is not significant.
- Substantial cross-over of those from the conservative arm to the surgical arm occurred, perhaps nullifying any potential difference in this ITT analysis.

Nimodipine in subarachnoid haemorrhage

BRANT: BRitish Aneurysm Nimodipine Trial. A randomized, controlled, double-blind trial assessing the efficacy of oral nimodipine at reducing cerebral infarction in subarachnoid haemorrhage.

AUTHORS: Pickard JD, Murray GD, Illingworth R *et al*.

REFERENCE: *BMJ* (1989) **298**, 636–42.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Oral nimodipine reduces cerebral infarction, and thereby improves outcome, following aneurysmal subarachnoid haemorrhage (SAH).

Impact

Oral nimodipine 60mg every 4h for 21d is given routinely to patients following aneurysmal SAH.

Aims

Cerebral ischaemia/infarction is a common, debilitating complication of aneurysmal SAH. Clinical studies investigating the effect of the calcium channel antagonist nimodipine on the incidence of this were inconclusive. Therefore, this study aimed to establish the effect of nimodipine on the incidence of cerebral ischaemia/infarction and subsequent outcome of aneurysmal SAH.

Methods

Patients: 554 (four centres in the UK).

Inclusion criteria:

- Aged ≥ 18 y;
- Within 96h of onset of aneurysmal SAH;
- Proven SAH on lumbar puncture and/or CT;
- Presence of an aneurysm subsequently proven on angiography or necropsy, or, in two cases, the typical appearance of a giant aneurysm on CT;
- Absence of major renal and pulmonary disease, pre-existing cardiac decompensation, or recent MI.

Groups:

- Nimodipine ($n = 278$, oral, 60mg every 4h for 21d);
- Placebo ($n = 276$).

Follow-up: 3mo.

Primary endpoint: Incidence of cerebral infarction.

Secondary endpoints:

- Outcome at 3mo: GOS;
- Adverse reactions.

Results**Table 25.4** Summary of result

| Primary endpoint | Nimodipine | Placebo | p |
|----------------------------------|------------|---------|--------|
| Incidence of cerebral infarction | 22% | 233% | 0.03 |
| Secondary endpoints | | | |
| Poor outcomes* | 20% | 33% | <0.001 |
| Death | 43 | 60 | <0.06 |
| Adverse reactions | 17 | 10 | |

* Poor outcome being death, vegetative state, and severe disability.

- Adjusting for prognostic factors, such as sex and loss of consciousness, did not change the significant reduction in cerebral infarction and poor outcome associated with nimodipine. Adverse events included CV (hypotension, flushing) and liver effects. They were sufficiently severe for eight patients in the nimodipine group, and three patients in the placebo group, to have medication withdrawn. (See Table 25.4.)

Discussion

This trial provides convincing evidence that nimodipine significantly reduces cerebral infarction and improves outcome, following aneurysmal SAH. Although cerebral ischaemia classically occurs between 7 and 10d following SAH, the need for early and prolonged institution of nimodipine is reflected by only 37% of ischaemic events in this trial occurring within this time frame. Furthermore, this trial specifically analyses SAH 2° to aneurysmal rupture. The results should not be extrapolated to SAH of other causes where evidence supporting the benefit of nimodipine is lacking.

Problems

- Treatment was discontinued in 130 patients (70 in the nimodipine group and 60 in the placebo group). The main reason was due to the absence of an aneurysm on angiography. It does not seem that these patients were then excluded from statistical analysis.

Coiling or clipping for ruptured intracranial aneurysms

ISAT: International Subarachnoid Aneurysm Trial. A randomised controlled trial assessing the effect of endovascular coiling vs surgical clipping for treating ruptured intracranial aneurysms.

AUTHORS: Molyneux AJ, Kerr RS, Yu LM et al.

REFERENCE: *Lancet* (2005) **366**, 809–17.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In a specific population with aneurysmal SAH, endovascular coiling is associated with less death and disability, compared to surgical clipping. Over time, the survival advantage remains, though that of disability is lost. Overall, coiling is associated with a greater risk of rebleeding. It may be that, in those of a younger age group, the robustness of surgical clipping outweighs its initial risk.

Impact

Results from ISAT are widely debated throughout the world. Overall, particularly in Europe, there has been a shift in practice favouring coiling.

Aims

A ruptured cerebral aneurysm causing SAH can be treated by surgical clipping or endovascular coiling, with the goal of aneurysm obliteration, thereby preventing further rebleeding, which is associated with high morbidity and mortality. This is the first RCT that compares the safety and efficacy of these approaches.

Methods

Patients: 2,143 (multicentre, international, 9,278 assessed for eligibility).

Inclusion criteria:

- SAH due to an intracranial aneurysm;
- Uncertainty principle: Surgeon uncertain of the preferable treatment.

Groups:

- Neurosurgical clipping ($n = 1,070$, 39 had coiling as the first procedure, 19 died prior to the first procedure);
- Endovascular coiling ($n = 1,073$, nine underwent clipping prior to coiling, seven died prior to the first procedure).

Follow-up: 2mo, 1y, and annually thereafter.

Primary endpoint: Death or dependence (modified Rankin Scale 3–6).

Secondary endpoint: Rate of rebleeding from the treated aneurysm.

Results

- Interim results reported in the original 2002 paper were incomplete, in terms of 1y F/U—the full set is reported here;
- The ARR of death or dependency at 1y is 7.4% in favour of coiling (3.6–11.2). (See Table 25.5.)

Table 25.5 Summary of result

| Primary endpoint | Surgical clipping | Endovascular coiling | RRR (95% CI) |
|--------------------|-------------------|----------------------|-------------------|
| Dead or dependent | 30.9% | 23.5% | 23.9% (12.4–33.9) |
| Secondary endpoint | | | |
| Rebleeding rate | 39 | 45 | 1.15 (0.75–1.75) |

Discussion

The ISAT trial has led to great controversy and debate worldwide. It seems that, in the short term, endovascular coiling is superior to surgical clipping of ruptured aneurysms, as it is associated with a lower risk of death or dependence, and, though there is an increased risk of rebleeding in the coiling group, this is small. Furthermore, though not randomized, this benefit has also been shown in the more recent USA-based BRAT study. However, 5y F/U of the ISAT cohort shows that, although there is an increased risk of death with clipping (RR 0.77, $p = 0.03$), with patients mainly dying from CV disease or cancer, there was no significant difference between the proportion of survivors independent at 5y with clipping, compared with coiling (82% vs 83%, respectively, $p = 0.61$). Importantly, when considering the actual treatment received, coiling was associated with significantly more rebleeding episodes than clipping (ten episodes after 1y in 8,447 person-years vs three episodes after 1y in 8,177 person-years, one of whom actually received coiling, respectively; log rank = 0.02). The durability of coiling over time remains unclear (see below)—in a related publication, ISAT investigators concluded that, in those aged <40y, the short-term advantage of coiling may not outweigh the risk of late rebleeding.

Problems

- The trial population was extremely specific: those of good clinical grade, with small anterior circulation aneurysms, amenable to both clipping and coiling; therefore, extrapolation of the ISAT data beyond this population requires some caution.
- More of those who underwent coiling required a further procedure in the first year, compared to those who underwent clipping (121 vs 33), and were more likely to require re-treatment >3mo post-bleed (HR 6.9, 95% CI 3.4–14.1). Consistent with this, fewer coiling patients had complete occlusion of their aneurysm, compared with clipping patients (66% vs 82%). However, these subgroup analyses were not prespecified, and 89% of coiling patients had F/U angiograms vs only 47% of clipping patients. Therefore, although the question of the effectiveness of coiling is raised, it is not yet adequately answered.

Extracranial–intracranial bypass surgery for stroke prevention

COSS: The Carotid Occclusion Surgery Study: Extracranial–intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia.

AUTHORS: Powers WJ, Clarke WR, Grubb RL et al.

REFERENCE: *JAMA* (2011) **306**, 1983–92.

STUDY DESIGN: Randomized, open-label trial.

EVIDENCE LEVEL: 1c.

Key message

The effect of extracranial–intracranial (EC–IC) bypass surgery on preventing stroke in adequately selected patients with internal carotid occlusion and ipsilateral cerebral hemispheric hypoperfusion has yet to be appropriately addressed.

Impact

Unfortunately, this study has been interpreted to show definitively no advantage of surgery over medical management for stroke prevention. Hence, reperfusion surgery is rarely performed.

Aims

EC–IC bypass surgery was developed to prevent subsequent stroke in those with atherosclerotic internal carotid artery (ICA) occlusion by improving haemodynamics distal to the occluded artery. However, the EC–IC bypass trial in 1985 demonstrated no benefit to surgery. This trial failed to identify the subgroup of patients with haemodynamic cerebral ischaemia due to poor collateral circulation for whom surgical revascularization would be of the greatest benefit. COSS attempts to identify this population, then assesses whether EC–IC bypass confers any additional advantage in stroke prevention over best medical therapy in this group.

Methods

Patients: 195 (67 centres in the USA and Canada).

Inclusion criteria:

- TIA or ischaemic stroke in the hemispheric territory of an occluded ICA in the preceding 120d;
- Intra-arterial catheter arteriography documenting occlusion of the symptomatic ICA, and intracranial and extracranial arteries suitable for anastomosis;
- Ipsilateral:contralateral ratios of mean regional carotid territory O_2 extraction fraction (OEF) >1.130 , measured by positron emission tomography (PET) imaging.

Groups:

- Surgery ($n = 97$, four of whom crossed over to medical management);
- Medical management ($n = 98$, three of whom crossed over to surgery).

Follow-up: 30–60d post-operatively, then at 3-monthly intervals until 24mo or the end of the trial.

Primary endpoint: Combination of all stroke and death from time of surgery or of randomization, through to 30d after surgery or after randomization; and ipsilateral ischaemic stroke within 2y of randomisation, expressed as a rate, based on product limit estimates of 2y rates and their SEs.

Secondary endpoints:

- All stroke, disabling stroke, fatal stroke, and death;
- NIHSS;
- Modified Barthel Index and modified Rankin Scale;
- Stroke-specific quality of life (SS-QOL) assessment.

Results

Table 25.6 Summary of result

| | Surgery | Medical management | <i>p</i> |
|------------------|----------------------|------------------------|----------|
| Primary endpoint | 21% (<i>n</i> = 20) | 22.7% (<i>n</i> = 20) | 0.78 |

- There was also no significant difference in the secondary endpoints between the two groups. On account of a futility analysis conducted after 194 participants had been randomized and 139 participants had 2y F/U, the trial was terminated early. (See Table 25.6.)

Discussion

EC–IC bypass in those with haemodynamic ischaemia from an occluded carotid artery does not seem to confer an advantage over best medical therapy in stroke prevention. However, before drawing such a conclusion, there are some important considerations, as below.

Problems

- This study was underpowered. The power calculation assumed a primary outcome rate of 40% in the non-surgical group, based upon a prospective observational study of similar patients carried out from 1992 to 1997. The actual stroke rate in COSS was almost half of this and consistent with more recent studies; the improvement consistent with advances in medications.
- Increased OEF is the gold standard measure of ischaemic stress and an independent predictor of increased stroke risk. COSS uses a qualitative OEF ratio, which has been shown not to identify the same patients at increased stroke risk, as indicated by the quantitative OEF. Hence, the very patients that may have benefited from surgical reperfusion were not necessarily selected in this study.

Decompressive surgery for spinal metastases

Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial

AUTHORS: Patchell RA, Tibbs PA, Regine WF *et al.*

REFERENCE: *Lancet* (2005) **366**, 643–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Surgery followed by RT is markedly superior to RT alone for spinal cord compression 2° to spinal metastases.

Impact

Patients with a single spinal metastasis causing spinal cord compression should now be referred to neurosurgery for consideration of spinal decompression, rather than immediate referral to radiation oncology.

Aims

Spinal cord compression due to metastasis is a common and debilitating complication of cancer. Previous trials did not support the role of decompressive laminectomy, demonstrating no benefit over radiation alone. However, another surgical procedure where the tumour is removed, resulting in immediate circumferential decompression, showed benefit over radiation in uncontrolled series and meta-analyses. This trial tests this technique in a randomized, controlled setting.

Methods

Patients: 101 (multicentre).

Inclusion criteria:

- ≥18y old;
- Tissue-proven diagnosis of cancer (not of CNS or spinal column origin);
- At least one neurological symptom or sign;
- Not totally paraplegic for longer than 48h prior to surgery;
- Single spinal metastasis causing spinal cord compression;
- An expected survival of at least 3mo;
- General medical status acceptable for surgery.

Groups:

- Surgery plus radiotherapy ($n = 50$, four had no/complete RT);
- RT alone ($n = 51$, ten crossed over to surgery following substantial decline in motor strength during RT).

Follow-up: Assessment every 4wk, until the end of the trial or death. Median F/U was 102d for surgery and 93d for radiation.

Primary endpoint: Maintenance of, or gaining, the ability to walk, i.e. able to take at least two steps with each foot unassisted, even if a cane or walker is needed, after treatment.

Secondary endpoints: Please see below.

Results

Table 25.7 Summary of result

| Primary endpoint | Surgery + RT | RT | p |
|---|--------------|-------|--------|
| Ability to walk after treatment | 84% | 57% | <0.001 |
| Secondary endpoints | | | |
| Continence maintained | 156d | 17d | 0.016 |
| Improved or maintained function post-treatment | 86% | 60% | 0.0064 |
| Improved or maintained muscle strength post-treatment | 91% | 61% | 0.0008 |
| Median dexamethasone equivalent dose | 1.6mg | 4.2mg | 0.0093 |
| Median opioid equivalent dose | 0.4mg | 4.8mg | 0.002 |
| 30d mortality rate | 6% | 14% | 0.32 |
| Median hospital stay | 10d | 10d | 0.86 |

Discussion

The clear superiority of surgery and RT over RT alone led to premature closure of the trial. Of note, preoperative neurology between the two groups was similar, and subgroup analysis of those who were able and not able to walk at study entry also reflected the significant benefit of surgery (data not shown). Importantly, surgery did not lead to an increase in hospital stay. This is overwhelming evidence supporting decompressive surgery for those with single spinal metastases causing spinal cord compression. (See Table 25.7.)

Problems

- Strict inclusion and exclusion criteria lead to a selection bias where only patients hypothesized to do well post-surgery are chosen for randomization.
- Neurological assessments were unblinded. However, the reasonable F/U period should have compensated for this.
- No standard surgical protocol was followed. However, there was a common aim—to provide direct circumferential decompression of the spinal cord and to provide spinal stabilization where necessary.

Radiosurgery and brain metastases

RTOG 9508: an RCT assessing whether the addition of a radiosurgery boost to whole-brain radiotherapy confers a survival advantage to those with 1–3 brain metastases.

AUTHORS: Andrews DW, Scott CB, Sperduto PW et al.

REFERENCE: *Lancet* (2004) **363**, 1665–72.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Radiosurgery boost treatment confers a survival advantage and improves functional autonomy in those with a single unresectable brain metastasis.

Impact

Those with a single unresectable brain metastasis should now be considered for radiosurgery boost treatment, in addition to whole-brain radiotherapy (WBRT).

Aims

Brain metastases are the commonest intracranial tumour. Prognosis is poor, with a median survival of 1–2mo. Survival can be extended to 6mo with WBRT and may be improved further, if WBRT is preceded by surgical resection. Stereotactic radiosurgery (SRS) may be preferred as a less invasive alternative to surgery in those unfit for surgery or those with unresectable metastases in deep-seated or eloquent parts of the brain. This trial assesses the additional benefit conferred by SRS to those with 1–3 unresectable brain metastases receiving WBRT.

Methods

Patients: 331 (from multiple RTOG institutions).

Inclusion criteria:

- Aged 18y or over, with no previous cranial irradiation;
- Contrast-enhanced MRI showing 1–3 unresectable brain metastases, outside of the brainstem or >1cm from the optic apparatus, with a maximum diameter of 4cm for the largest lesion and additional lesions not exceeding 3cm in diameter;
- Treatment for systemic cancer completed >1mo ago;
- Karnofsky performance score (KPS) >70.

Groups:

- WBRT plus SRS boost ($n = 164$, radiosurgery given within 1wk of completing WBRT);
- WBRT alone ($n = 167$).

Follow-up: 3, 6, 9, and 12mo.

Primary endpoint: Overall survival (subgroup analysis including survival by number of brain metastases, analysis of potential prognostic factors).

Secondary endpoints:

- Overall time to tumour progression;
- Local control rate;
- Performance measures (KPS, steroid use, mental status).

Results**Table 25.8** Summary of result

| Primary endpoint | WBRT + SRS | WBRT alone | p |
|---------------------------------------|------------|------------|--------|
| Overall survival | 6.5mo | 5.7mo | 0.1356 |
| Survival with single brain metastasis | 6.5mo | 4.9mo | 0.0393 |
| Secondary endpoints | | | |
| Time to tumour progression | | | 0.1278 |
| Overall local control | 82% | 71% | 0.0132 |

- Early and late toxicities did not differ between groups. The rate of neurological deaths did not differ between groups. Univariate and multivariate analysis revealed that recursive partitioning analysis (RPA) class and tumour type were prognostic factors, independent of metastasis number, with RPA class 1 and squamous and non-small cell carcinomas having significantly better outcomes with the addition of SRS. SRS also conferred a statistically significant improvement in KPS and decreased steroid use at 6mo. There was no difference in mental status noted between the groups. (See Table 25.8.)

Discussion

Addition of SRS to WBRT improves survival, local control rates, and performance measures in those with a single unresectable brain metastasis. It should be considered in all presenting likewise, and especially in those deemed RPA class 1 and those with squamous or non-small cell tumours. As SRS improved performance measures in all patients, it may still be considered in those with multiple brain metastases. Trials comparing surgery and SRS failed to accrue enough patients, due to strong biases of treating physicians and informed patients. However, there are ongoing trials comparing SRS alone with WBRT plus SRS.

Problems

- A total of 31 patients (19%) of the SRS group did not receive SRS, and, as this was an ITT analysis, this group was still analysed as having had SRS, thus potentially affecting outcome.
- A significant number of MRIs were not available for assessment at 3mo F/U, thereby affecting the analysis of secondary outcomes.

Adjuvant temozolomide for grade 4 astrocytoma

An RCT assessing the addition of temozolomide to focal radiotherapy for the treatment of grade 4 astrocytoma.

AUTHORS: Stupp R, Mason WP, van den Bent MJ *et al.*

REFERENCE: *N Engl J Med* (2005) 352, 987–96.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Addition of temozolomide to RT confers a significant survival advantage to those with grade 4 astrocytoma, with minimal toxicity.

Impact

Temozolomide is now used as routine adjuvant therapy for those with grade 4 astrocytoma.

Aims

Grade 4 astrocytoma is the commonest adult 1° brain tumour. Despite surgical resection and RT, prognosis remains poor, with a median survival of 1y from diagnosis. Temozolomide, an alkylating agent that depletes the DNA repair enzyme O-6-methylguanine DNA methyltransferase (MGMT), has been shown to potentially improve survival in phase 2 studies. This randomized, controlled phase 3 trial aims to substantiate this finding.

Methods

Patients: 573 (85 centres in 15 countries).

Inclusion criteria:

- Aged between 18 and 70y;
- Histologically confirmed WHO grade 4 astrocytoma;
- WHO performance status of 2 or less;
- Adequate haematologic, renal, and hepatic function;
- Those receiving a stable or decreasing dose of corticosteroids.

Groups:

- RT plus temozolomide ($n = 287$, daily temozolomide during RT, followed by six cycles of adjuvant temozolomide);
- RT only ($n = 286$).

Follow-up: overall 2y.

Primary endpoint: Overall survival.

Secondary endpoints:

- PFS;
- Safety.

Results

Table 25.9 Summary of result

| Primary endpoint | RT + temozolomide (95% CI) | RT alone (95% CI) |
|----------------------------------|----------------------------------|--------------------|
| Median survival | 14.6mo (13.2–16.8) | 12.1mo (11.2–13.0) |
| 2y survival rate | 26.5% (21.2–31.7) | 10.4% (6.8–14.1) |
| Secondary endpoints | | |
| Median PFS | 6.9mo (5.8–8.2) | 5mo (4.2–5.5) |
| Grades 3–4 haematologic toxicity | Concomitant: 7% Adjuvant: 14% | 0% |
| Severe infections | Concomitant: 3% Adjuvant: 5% | 2% |

- At 28mo, 480 patients had died. The HR for death in the RT plus temozolomide group, compared to the RT alone group, was 0.63 ($p < 0.001$). The HR for death or disease progression was 0.54 ($p < 0.001$), in favour of the group receiving temozolomide. (See Table 25.9.)

Discussion

This study demonstrates that the addition of the chemotherapeutic agent temozolomide to RT significantly prolongs the survival of patients with newly diagnosed grade 4 astrocytoma, with a median increase in survival of 2.5mo or a relative reduction in risk of death by 37%. Furthermore, chemotherapy is safe, with minimal toxicity. Interestingly, a companion paper demonstrates that, in patients in whom the MGMT promoter is methylated, resulting in gene silencing, not only was survival significantly improved, irrespective of treatment assignment, but the response to temozolomide was also significantly enhanced. More recently, mutations of the isocitrate dehydrogenase 1 (*IDH1*) gene have also been found to confer a survival advantage in 2° grade 4 astrocytomas, i.e. those that transform from low-grade gliomas, as opposed to those that develop *de novo*. In one paper, the presence of an *IDH1* mutation was associated with a better response to temozolomide. However, this relationship does require further clarification.

Problems

- Eighty-five percent in the RT plus temozolomide group and 94% in the RT alone group had disease progression. At this time, further treatment was at the physician's discretion, which included surgery and salvage chemotherapy. Salvage therapies may have influenced the overall outcome in this ITT analysis.

Treatment of low-grade gliomas

Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas.

AUTHORS: Jakola AS, Myrnes KS, Kloster R et al.

REFERENCE: *JAMA* (2012) **308**, 1881–8.

STUDY DESIGN: Retrospective, parallel, cohort study.

EVIDENCE LEVEL: 3.

Key message

The best management of low-grade gliomas (LGGs) is not established. In the Norwegian population examined here, initial gross total resection (GTR) confers a significant survival advantage over biopsy and watchful waiting.

Impact

Despite the limitations of being retrospective, this carefully designed study does strengthen the support for early GTR of LGGs. Based on these results, both hospitals involved in this study now advocate early GTR to those with a new diagnosis of LGG.

Aims

LGGs are slow-growing 1° glial tumours. Though slow-growing, they are extremely invasive and commonly transform into high-grade lesions that are ultimately fatal. Considerable controversy exists regarding the best approach for LGGs. Although the majority of studies seem to support GTR, this is not unanimous. No randomized controlled studies have been conducted in this area and are unlikely in the future, due to the low incidence and the need for long F/U. Taking advantage of a unique situation in Norway where both the socialized delivery of health care and population are homogenous, and with the existence of two hospitals relatively close in geographic location with different treatment philosophies, one favouring initial biopsy and watchful waiting, and the other favouring initial GTR, this retrospective cohort study attempts to add more understanding to this problem.

Methods

Patients: 153.

Inclusion criteria:

- Adults ≥ 18 y, with histologically verified supratentorial WHO II diffuse LGGs.

Groups:

- Initial GTR ($n = 87$, 12 crossed over to initial biopsy);
- Initial biopsy ($n = 47$, 19 of whom crossed over to initial GTR).

Follow-up: 2y from the end of recruitment period, or until death, on average 7y.

Primary endpoint: Overall survival.

Secondary endpoints: Surgical morbidity.

Results

Table 25.10 Summary of result

| Primary endpoint | GTR | Biopsy only | <i>p</i> |
|-----------------------|-----|-------------|----------|
| Overall survival | 68% | 48% | 0.01 |
| Secondary endpoint | | | |
| Surgical complication | 9% | 8% | 0.82 |

- Median survival at the centre favouring biopsy was 5.9y (95% CI 4.5–7.3), while it has not yet been reached at the centre favouring initial resection. Post hoc analysis revealed no difference in the number of acquired deficits between centres (18% vs 21%, $p = 0.7$). Malignant transformation was commoner, when biopsy only was the favoured initial management (56% vs 37%, $p = 0.02$). (See Table 25.10.)

Discussion

For patients in Norway with LGG, early GTR over biopsy seems to confer a survival benefit. Although such a retrospective study is full of hazards, some bias can be compensated for by the unique situation of health care there (see below). Although extrapolation to a more generalized population requires caution, these results are consistent with those elsewhere, adding weight towards early GTR. RCTs are also not without their own limitations and this carefully conceived study illustrates the potential contribution from well-designed cohort analyses.

Problems

- Without randomization, this study is open to referral bias. With a homogenous population and uniform provision of health care, there is an almost perfect correlation between the site of residence and receipt of treatment, eliminating this risk.
- Although a lack of randomization does open this study to significant bias, the primary endpoint was a hard clinical endpoint, i.e. overall survival. Furthermore, a regional comparison of overall survival was made, eliminating the selection bias of an as-treated analysis.
- Importantly, there were more patients with oligodendrogliomas in the initial resection group vs the initial biopsy group (19% vs 9% respectively), and oligodendrogliomas have a 5y survival of 80% vs 50% for astrocytomas. However, subgroup analysis of those with low-grade astrocytomas also shows that initial resection confers a survival advantage over initial biopsy (median survival 9.7y vs 5.6y, $p = 0.05$, respectively).
- Caution should be used when interpreting outcomes other than survival, as there was no standardized F/U or blind review of data, opening interpretation to detection bias.

Surgery for lower back pain

A randomized controlled trial comparing surgical stabilization of the lumbar spine with an intensive rehabilitation programme for chronic lower back pain.

AUTHORS: Fairbank J, Frost H, Wilson-MacDonald J *et al.*

REFERENCE: *BMJ* (2005) **330**, 1233–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the first randomized trial to address the efficacy of surgery, compared to intensive rehabilitation, for lower back pain. It demonstrates no clear evidence in support of surgical intervention.

Impact

In patients suffering from lower back pain, a period of intensive rehabilitation should be considered before surgical intervention.

Aims

Chronic back pain is a common and debilitating condition. Although about 1,000 lumbar fusions are performed per year in England, no clear evidence exists to support this practice over conservative management. This trial was designed to compare the efficacy of surgical stabilization with an intensive rehabilitation programme, for symptom relief in patients with chronic lower back pain.

Methods

Patients: 349 (15 centres across the UK).

Inclusion criteria:

- Aged between 18 and 55y;
- >12mo history of lower back pain;
- Uncertainty principle: Those deemed suitable for spinal stabilization, but uncertainty of the clinician and patient which treatment strategy would be best;
- No other co-morbidities making one of the trial interventions unsuitable, e.g. inflammatory disease, tumours, fractures.

Groups:

- Surgical stabilization ($n = 176$, 4% crossed over to rehabilitation);
- Intensive rehabilitation programme ($n = 173$, 28% crossed over to surgery).

Follow-up: 6, 12, and 24mo. Note overall 20% lost to F/U.

Primary endpoint:

- QoL (Oswestry disability index, ODI);
- Shuttle walking test: Standardized, progressive, maximal test of walking speed and endurance.

Secondary endpoints:

- Physical health, e.g. physical functioning, role limitation (SF36);
- Mental health, e.g. social functioning, energy, and vitality (SF36).

Results**Table 25.11** Summary of result

| Primary endpoints | Estimated difference (95% CI) | p |
|----------------------------|-------------------------------|------|
| ODI | -4.1 (-8.1 to -0.1) | 0.04 |
| Shuttle walking test | 34 (-8 to 77) | 0.12 |
| Secondary endpoints | | |
| SF36 physical | 2.0 (-1.2 to 5.3) | 0.21 |
| SF36 mental | -0.2 (-2.9 to 2.6) | 0.90 |

- 24mo F/U;
- Intraoperative complications occurred in 19 surgical cases; 11 patients required further operative intervention during the F/U period. Rehabilitation was not associated with any specific complications. (See Table 25.11.)

Discussion

Surgery seems to be significantly better at improving back pain than rehabilitation. However, the difference of 4.1 points represents a very small clinical difference. And, in the face of all other outcomes being non-significant, this result requires cautious interpretation. When also considering the complications and costs associated with surgery, overall the evidence supporting spinal stabilization for back pain is lacking.

Problems

- Selection bias is introduced by only randomizing patients deemed suitable for spinal stabilization.
- There is a lack of blinding in the F/U assessment, although overall scores from the questionnaires were calculated centrally.
- Significant numbers were lost to F/U (20%), challenging the internal validity of the trial, although statistical analyses adjusting for this loss yielded similar results to the above.
- A significant number of patients allocated to rehabilitation crossed over to surgery during the F/U period, and, as this was an ITT analysis, these patients were considered as part of the control group, with a potential impact on the overall result.

Instrumentation for spondylolisthesis

A randomized controlled trial comparing decompressive laminectomy and arthrodesis with and without spinal instrumentation for degenerative lumbar spondylolisthesis.

AUTHORS: Fischgrund JS, Mackay M, Herkowitz HN et al.

REFERENCE: *Spine* (1997) 22, 2807–12.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In those who fail conservative therapy, arthrodesis, with or without instrumented fusion, is an effective and safe treatment for symptomatic spinal stenosis 2° to lumbar spinal spondylolisthesis.

Impact

Without a consensus on the best method of spinal fusion, guidelines advise pedicle screw fixation be considered where there is preoperative evidence of spinal instability or kyphosis at the level of spondylolisthesis or when iatrogenic instability is anticipated.

Aims

Degenerative spondylolisthesis with resulting spinal stenosis can cause lower back pain and neurogenic claudication. Surgery for isolated lower back pain due to degenerative conditions requires caution. However, if there are neurological symptoms, then decompressive laminectomy effectively provides symptom relief. However, if used alone in the presence of spondylolisthesis, there is concern for progressive symptomatic deformity over time. Herkowitz (1991) conducted a prospective study showing that decompression with fusion across the transverse processes (arthrodesis) led to better outcomes. This study looks at whether the addition of instrumented fusion with pedicle screws is superior to arthrodesis (non-instrumented fusion) alone.

Methods

Patients: 68 (one centre in the USA).

Inclusion criteria:

- Clinical diagnosis of degenerative spondylolisthesis and spinal stenosis;
- Failed conservative management for at least 3mo;
- Diagnosis verified on plain X-rays and CT and/or MRI;
- No prior lumbar spinal surgery.

Groups:

- Decompression, arthrodesis, instrumented fusion ($n = 35$);
- Decompression and arthrodesis only ($n = 33$).

Follow-up: 2y.

Primary endpoints:

- Level of overall improvement (relief of back/leg pain, activity level);
- Successful arthrodesis.

Results**Table 25.12** Summary of result

| Primary endpoints | Test group | Control group | <i>p</i> |
|------------------------------------|------------|---------------|----------|
| Clinical outcome excellent or good | 78% | 85% | 0.45 |
| Successful arthrodesis | 82% | 45% | 0.0015 |

- Both groups had a significant improvement in back and/or leg pain, following surgery. No new neurological deficits or infections developed, following surgery. No patient required early removal of hardware. (See Table 25.12.)

Discussion

Arthrodesis, with or without instrumented fusion, is an effective and safe treatment for symptomatic spinal stenosis 2° to lumbar spinal spondylolisthesis in those who have failed conservative therapy. It seems that, although instrumentation results in significantly higher rates of fusion, this does not necessarily translate to a better clinical outcome. However, F/U (mean of 7y) of Herkowitz's and Fischgrund's patients showed that those with a solid fusion did subsequently have a better clinical outcome. More recently, the SPORT study, where patients were enrolled to randomized ($n = 304$) or observational cohorts ($n = 303$) and underwent standard decompressive laminectomy (with or without fusion) or usual non-surgical care, has been completed. The ITT analysis for the randomized cohort showing no statistically significant effects for primary outcomes was not interpretable in the face of high cross-over rates (40% in each direction). Though interpretation requires caution, consistent with previous studies, the as-treated analysis for both cohorts combined showed a significant advantage for surgery that persisted to 4y. Notably, patients receiving conservative treatment showed moderate improvement in all outcomes and came to no harm. Interestingly, there were no consistent differences in clinical outcome between the three fusion methods over 4y—intertransverse process arthrodesis alone; intertransverse process arthrodesis with pedicle screws; intertransverse process arthrodesis, pedicles screws, and interbody fusion.

Problems

- This is an unblinded study, although radiographic images were analysed by independent radiologists.
- In neither this study nor the other studies mentioned is an assessment made of stability at the level of the spondylolisthesis with flexion–extension films. As there is no clear consensus on the best fusion method, the presence or absence of instability may be helpful in deciding the lengths that are needed to go to, in order to achieve a solid fusion (see Impact).

Surgery for lumbar disc herniation

SPORT (The **S**pine **P**atient **O**utcomes **R**esearch **T**rial): Surgical vs non-operative treatment for lumbar disk herniation.

AUTHORS: Weinstein JN, Tosteson TD, Lurie JD *et al.*

REFERENCE: *JAMA* (2006) **296**, 2441–50.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Both surgical and conservative management of lumbar radiculopathy 2° to disc herniation are both effective and safe. Superiority of one treatment over the other is yet to be definitively established.

Impact

In assessing such patients, where there are no complicating factors such as cauda equina syndrome or weakness, conservative management as first-line therapy is entirely reasonable.

Aims

Lumbar radiculopathy 2° to disc herniation is a common problem. Most patients who do not have cauda equina syndrome or progressive weakness are initially managed medically. However, if symptoms persist and become intolerable, surgical discectomy is usually recommended. However, the benefit of surgery over conservative management is by no means established. This trial aims to assess the efficacy of surgery, compared to conservative management. It consists of two parallel studies: the first a randomized controlled study which is presented here, and the second an observational cohort study of the patients who declined enrolment into the randomized study.

Methods

Patients: 501 (13 centres in the USA).

Inclusion criteria:

- Aged ≥ 18 y, with persistent (≥ 6 wk) symptoms and signs of radiculopathy 2° to intervertebral disc herniation that is demonstrated on MRI or CT, and no history of prior surgery;
- No evidence of cauda equina syndrome, fracture, infection, inflammation, or tumour.

Groups:

- Surgery with open discectomy ($n = 232$ patients, 40% crossed over);
- Conservative management ($n = 240$ patients, 45% crossed over).

Follow-up: 6wk, 3mo, 6mo, 1y, and 2y.

Primary endpoint: Changes from baseline in the:

- SF36 bodily pain and physical function scales;
- MODEMS version of the ODI.

Secondary endpoints:

- Symptom severity as per the Sciatica Bothersomeness Index (SBI);
- Self-reported improvement, work status, and satisfaction with care.

Results**Table 25.13** Summary of result

| Primary endpoints | Surgery | Conservative | Treatment effect (95% CI) |
|------------------------|---------|--------------|---------------------------|
| SF36—bodily pain | 40.3 | 37.1 | 3.2 (−2.0 to 8.4) |
| SF36—physical function | 35.9 | 35.9 | 0 (−5.4 to 5.5) |
| ODI | −31.4 | −28.7 | −2.7 (−7.4 to 1.9) |

- Importantly, both treatment groups showed strong improvements at each of the designated time points. However, at no time point is surgery seen to confer a significant benefit over conservative management in the primary or secondary endpoints (2y data presented). The exception is with the SBI where surgery did confer a significant benefit at all time points. Surgery did confer a benefit at 1y for self-rated progress, but this did not carry out to 2y. Such results also persisted to 4y. As-treated analyses showed a strongly significant advantage with surgery at all time points, which also persisted to 4y. Notably, there is little evidence of harm from either treatment—no patient in either group developed cauda equina syndrome. (See Table 25.13.)

Discussion

Consistent with conclusions of previous studies, this trial demonstrates that patients improve with either medical or surgical therapy, and reassuringly both strategies are safe. The ITT analysis failed to show that surgery conferred any additional benefit, although the as-treated analysis did. Moreover, the results of the as-treated analysis are consistent with that of the observational cohort. However, in view of the problems below, overall results are inconclusive.

Problems

- The ITT analysis is limited by the large cross-over from each group and also by significant differences between the groups that crossed over, the nature of which could have underestimated the true effect of surgery.
- As-treated analyses are limited by selection bias, and results should be interpreted with caution. Furthermore, selection bias was compounded by the fact that patients could choose between being in the randomized trial or in the observational cohort.
- This trial assumes all conservative strategies to be equivalent, for which there is no evidence, and the patients who were randomized were those who had already failed conservative therapy, thereby biasing results in favour of surgery.

Surgery for Parkinson's disease

A randomized trial of deep-brain stimulation in the earlier stages of Parkinson's disease.

AUTHORS: Schüpbach WM, Maltête D, Houeto JL et al.

REFERENCE: *Neurology* (2007) **68**, 267–71.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Bilateral subthalamic nucleus (STN) stimulation early in the course of PD improves QoL.

Impact

STN stimulation should be considered in younger patients with PD, who are still in employment and in whom the disability of this chronic and progressive disease may be postponed.

Aims

Strong evidence supports bilateral STN stimulation for advanced PD. However, data assessing the impact of neurostimulation earlier in the disease process are scant. Early STN stimulation in younger patients with more recent disease onset may improve QoL and prevent psychosocial degradation that negatively impacts on productivity.

Methods

Patients: 20 (enrolled, matched and randomized in pairs).

Inclusion criteria:

- <55y;
- Duration of PD of 5–10y;
- Mild to moderate motor symptoms;
- Motor fluctuations with 'off periods' during >25% of the day;
- A professional activity of any kind;
- Normal brain MRI;
- Absence of severe psychiatric disease and dementia;
- Impaired social and occupational functioning due to PD.

Groups:

- Bilateral STN stimulation ($n = 10$);
- Best medical treatment, adapted to each patient ($n = 10$).

Follow-up: At 6, 12, and 18mo.

Primary endpoint: Relative change in the overall QoL (PDQ39).

Secondary endpoints:

- Impact on ADLs (UPDRS II);
- Severity of motor disability: Examinations were conducted unblinded, both 'off' and 'on' medication (UPDRS III);

- Reduction in daily dose of L-dopa equivalence;
- Levodopa-induced motor complications (UPDRS IV);
- Cognition, frontal lobe function, anxiety, and psychiatric morbidity (CPRS, MADRS, BAS).

Results

Table 25.14 Summary of result

| Primary endpoint | Surgery | Medical | <i>p</i> |
|--|---------|---------|----------|
| Improved QoL | 24% | 0% | <0.05 |
| Secondary endpoints | | | |
| Improved ADLs | −27% | 28% | <0.05 |
| Improved severity of motor disability 'off medication' | −29% | 69% | <0.05 |
| Reduction in daily dose of L-dopa | −12% | 57% | <0.05 |
| Improved L-dopa-induced motor complications | −15% | 83% | <0.05 |

- Motor scores 'on' medication did not change for groups. Cognition and frontal lobe function remained stable in both groups. Anxiety and psychiatric morbidity improved significantly in the surgical group, with no change in the medical group. Five patients had transient hypomania after surgery; four surgical vs three medical patients had transient depression during F/U. One surgical patient had the lead cable severed at implantation. (See Table 25.14.)

Discussion

This is the first randomized study to address early STN stimulation for mild to moderate symptoms of PD early in the course of illness. Adverse effects of surgery were mostly mild and transient. The low complication rate may be due to the younger trial group. The marked benefit of surgery over medical therapy and its relative safety make STN stimulation an option in those with PD before severe motor disability and L-dopa-associated motor effects develop.

Problems

- This is an unblinded, open-label study, as sham surgery was considered unethical. However, it would be unlikely for any placebo effect of surgery to persist for 18mo.
- Although a very small trial, there were enough subjects to power the study. However, the results require validation in a larger multicentre study.
- 18mo is a short F/U for a disease that can span decades. Long-term F/U is essential to assess the durability of STN stimulation and its effect on disease progression.

Surgery for temporal lobe epilepsy

A randomized, controlled study of surgery for temporal-lobe epilepsy.

AUTHORS: Wiebe S, Blume WT, Girvin JP *et al.*

REFERENCE: *N Engl J Med* (2001) **345**, 311–18.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the first randomized trial to demonstrate that surgery is superior to prolonged medical therapy in treating temporal-lobe epilepsy (TLE).

Impact

Based upon these results, the American Academy of Neurology recommends surgery as the treatment of choice for medically intractable TLE.

Aims

Epilepsy is a relatively common and debilitating condition, affecting a young working population. Medical therapy is limited by SEs, drug interactions, and need for monitoring. Advances in neuroimaging and surgical technique make surgical treatment more feasible. However, little robust evidence exists to support its safety and efficacy. This study aims to demonstrate that surgical management of TLE is both as efficacious and safe as medical therapy.

Methods

Patients: 80 (one university centre in Canada).

Inclusion criteria:

- ≥ 16 y;
- Seizures with strong temporal-lobe semiology for >1 y: Assessed by an epileptologist, MRI, EEG, and neuropsychology;
- Poorly controlled seizures with medication: Seizures occurring at least monthly, despite two or more anticonvulsants.

Groups:

- Surgery ($n = 36$; four subsequently did not undergo surgery);
- Medical ($n = 44$).

Follow-up: At 3, 6, and 12mo, by three epileptologists, two of whom were blinded to the treatment group.

Primary endpoint: Freedom from seizures impairing awareness, i.e. complex or partial seizures, at 1y.

Secondary endpoints: Free of all seizures, including auras; QoL.

Results

- Severity of seizures, the numbers attending school or who were employed, and depression were not significantly different between the two groups. (See Tables 25.15 and 25.16.)

Table 25.15 Summary of result

| Primary endpoint | Surgery | Medical | p |
|--|---------|---------|--------|
| Free of seizures impairing awareness at 1y | 58% | 8% | <0.001 |
| Secondary endpoints | | | |
| Free of all seizures, including auras | 38% | 3% | <0.001 |
| QoL* | 73.8 | 64.3 | <0.001 |

* Adjusted mean global scores on the Quality of Life in Epilepsy Inventory-89.

Table 25.16 Summary of result

| Adverse events | Surgery | Medical |
|----------------|---------------------|----------------|
| Other | One wound infection | 0 |
| Neurological | 25 (see below)* | 0 |
| Deaths | 0 | One unexpected |

* One small thalamic infarct causing sensory abnormalities in the thigh; two had a decline in verbal memory, affecting occupation, and 22 had asymptomatic superior subquadrantic visual field defects.

Discussion

This is the first robust evidence supporting surgery for the treatment of TLE. Although there were more neurological complications than with medical treatment alone, these were relatively minor. The benefits of surgery certainly outweigh the risks. Although the American Academy of Neurology subsequently recommended surgery as the treatment of choice for medically intractable TLE, the time to surgical referral has not decreased for undetermined reasons. In light of this, a USA-based randomized trial was designed to address whether earlier surgical treatment would be superior to medical therapy where the participants had no more than 2y of two anticonvulsants. The mean duration of seizures before enrolment was 10.9y vs 19.7y in the Wiebe *et al.* study. Although terminated early due to slow recruitment ($n = 38$), 0% of the medical group was seizure-free vs 85% of the surgical group ($p < 0.001$), reinforcing the benefit of surgery over medical therapy only in TLE.

Problems

- Those in the surgery group also received optimal medical therapy for the duration of F/U. It is unclear if medication had been reduced over this time. It would have been of interest to see if patients could have been rendered medication-free.
- F/U for 1y is a short period of time. However, there is evidence to suggest that seizure-related outcome at 1y, following temporal lobectomy, is a reasonable predictor of subsequent outcome.
- There is no indication of the effect of surgery on cognition. The USA-based study attempted to address this, but there were too few participants for meaningful data.

Obstetrics and gynaecology

- Introduction 708
- Tubal ectopic pregnancy: type of surgery 710
- Tubal ectopic pregnancy: methotrexate or surgery 712
- Recurrent miscarriage and antiphospholipid antibodies 714
- Unexplained recurrent miscarriage 716
- Prevention of preterm birth: cervical cerclage 718
- Pre-eclampsia: preventing seizures 720
- Preterm rupture of membranes and spontaneous labour: antibiotics 722
- Prelabour rupture of membranes: management at term 724
- Breech presentation: mode of delivery 726
- Hormone replacement therapy 728
- Polycystic ovary syndrome: metformin treatment 730
- Polycystic ovary syndrome: infertility treatment 732
- Uterine fibroids: embolization vs surgery 734

Introduction

The history of obstetrics and gynaecology is as old as the history of childbirth and, according to some obstetricians, perhaps even older. Evidence of dedicated and skilful aid during labour appears in ancient Hindu, Egyptian, Grecian, and Roman cultures. There are also less accurate records and legends. One of them says that the great Roman emperor Julius Caesar was born by the abdominal route, the procedure later named after him. This is unlikely to be true, as his mother Aurelia died at the age of 76; the first accurate record of a mother surviving a Caesarean dates from the nineteenth century, when lower segment sections and suturing of the incision became routine practice.

In the Middle Ages, childbirth and the practice of obstetrics were ripe with superstitions and secrecy. From the fourteenth to the seventeenth century, many midwives and ♀ healers were accused of being witches and were hunted and executed. Modern clinical governance processes tend to be less drastic.

In sixteenth-century London, two obstetricians, the Chamberlen brothers, revolutionized the management of obstructed labour by inventing obstetric forceps. However, their contribution to the EBM of the time is questionable, as the brothers went to great length to keep their invention a secret within the family. When they arrived at the home of the labouring woman, their assistants would carry a large box with a pair of forceps in it. Everybody had to leave the room, and the patient was blindfolded for the procedure. It was not until 130y later that the secret finally leaked out for the benefit of many. Fortunately, the results of clinical trials now have more urgent time frames.

Modern obstetricians and gynaecologists are less shy and secretive and more generous with their inventions, sharing them with their peers and patients alike. EBM is now deeply rooted in obstetrics and gynaecology, with many large, effective, and often multinational trials providing evidence to improve practice and the care of women.

Tubal ectopic pregnancy: type of surgery

Management of unruptured ectopic gestation by linear salpingostomy: a prospective randomized clinical trial of laparoscopy versus laparotomy.

AUTHORS: Vermesh M, Silva P, Rosen G *et al.*

REFERENCE: *Obstet Gynaecol* (1989) **73**, 400–4.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the first RCT to show similar efficacy and safety for laparoscopic linear salpingostomy vs routine laparotomy. However, laparoscopic procedures result in shorter recovery times and are more cost-effective.

Impact

The UK's Royal College of Obstetricians and Gynaecologists (RCOG) 2004 'Green Top' guidelines on the management of tubal pregnancy now quote a laparoscopic approach for the management of ectopic pregnancies as preferable to the open approach in haemodynamically stable patients.

Aims

Prompt management of tubal ectopic pregnancy is key to preserving fertility and reducing morbidity. With ultrasound and β -hCG assays often allowing diagnosis prior to rupture, linear salpingostomy by laparotomy had become an established procedure. Although laparoscopic approaches had been suggested to confer acceptable rates of subsequent intrauterine pregnancy and lower morbidity, a direct comparison of these two surgical approaches had yet to be undertaken. This study aimed to compare factors, including morbidity, fertility outcome, and cost, between laparoscopy and laparotomy for linear salpingostomy.

Methods

Patients: 60 women (80% Mexican-American, 10% white, 5% black, 5% Asian) at one centre in the USA.

Inclusion criteria: Women with ectopic pregnancy:

- Age >18y with a desire for future fertility;
- Stable vital signs and haematocrit >30%.

Exclusion criteria:

- Ruptured tube or diameter of tubal gestation >5cm;
- Location of ectopic other than the isthmus or ampulla;
- Presence of pelvic adhesions limiting visualization.

Groups:

- Laparoscopy ($n = 30$);
- Laparotomy (open surgery) ($n = 30$).

Primary endpoint: Safety-related complications (intraoperative and short-term).

Secondary endpoints:

- Efficacy-confirmed tubal patency at hysterosalpingography (HSG);
- Intraoperative blood loss;
- Cost and length of hospital stay;
- Pregnancy rates (in those seeking conception).

Follow-up: β -hCG levels every 3d, until level ≤ 1.5 mIU/L. HSG at 12wk.

Results**Table 26.1** Summary of results

| | Laparoscopy | Laparotomy | <i>p</i> |
|--|--------------------|--|----------|
| Primary endpoints (complications) | | | |
| Intraoperative | 2 cases* | 0 | – |
| Short-term | 1 post-op fever | 2 wound infections; 1 post-op fever | – |
| Secondary endpoints | | | |
| Patent HSG | 80% (16/20) | 89% (17/19) | ns |
| Mean intraoperative blood loss | 79mL (± 18) | 195mL (± 24) | <0.001 |
| Length of stay | 1.4d (± 0.1) | 3.3d (± 0.2) | <0.001 |
| Pregnancy rates | 56% (10/18) | 58% (11/19) | ns |

* The two cases requiring laparotomy (for haemostasis) both had gestations of 5cm in diameter.

- All pregnancies conceived within 6mo of surgery. (See Table 26.1.)
- Cost savings = US\$150/patient undergoing laparoscopy (vs laparotomy).

Discussion

Two subsequent RCTs have confirmed these findings (*Fertil Steril* (1992) 57, 998–1002, and *Fertil Steril* (1992) 57, 1180–5). In women who desired future fertility, the subsequent tubal patency and intrauterine pregnancy rates were similar between the open and laparoscopic groups. There was a trend towards lower repeat ectopic pregnancies if a laparoscopic approach was used, but also higher rates of persistent trophoblast.

Problems

- A total of 60 patients were recruited to this trial, and only 228 women were studied in total between all three relevant trials. This may be insufficient to look at small differences between the two interventions.
- All authorities agree that, in haemodynamically unstable situations, treatment should be by the most expedient route (e.g. salpingectomy, rather than a conservative method) and probably an open approach.

Tubal ectopic pregnancy: methotrexate or surgery

Randomised trial of systemic methotrexate versus laparoscopic salpingostomy in tubal pregnancy.

AUTHORS: Hajenius P, Engelsbel S, Mol B et al.

REFERENCE: *Lancet* (1997) 350, 774–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This RCT showed medical management with MTX to be as effective as laparoscopic salpingostomy in treating unruptured tubal pregnancies in stable women.

Impact

The UK's NICE guideline on ectopic pregnancy and miscarriage recommends that medical treatment with MTX should be offered as first-line treatment to women with unruptured tubal pregnancy <3.5cm with no visible heartbeat, β -hCG <1,500IU/L, and who are not in pain.

Aims

Laparoscopic salpingostomy is a well-established treatment in patients with tubal ectopic pregnancy who wish to retain their fertility. Another approach that preserves the integrity of Fallopian tubes is medical treatment with MTX. This study aimed to compare systemic MTX and laparoscopic salpingostomy in the treatment of tubal pregnancy.

Methods

Patients: 100 women at six centres in The Netherlands.

Inclusion criteria: Women with tubal ectopic pregnancy

Exclusion criteria:

- First stage: Unstable vital signs, ultrasound diagnosis of interstitial/cervical/ovarian/heterotopic pregnancy, contraindications to MTX or laparoscopic surgery;
- Second stage: Tubal rupture, active bleeding, no tubal pregnancy, impossibility of laparoscopic salpingostomy.

Groups:

- Laparoscopic salpingostomy ($n = 49$);
- MTX ($n = 51$).

Protocol:

- Patients were randomized prior to a confirmatory diagnostic laparoscopy. The 2° exclusion criteria were assessed by a surgeon unaware of the randomization decision;

- For those randomized to surgery, salpingostomy was undertaken after diagnosis confirmed at laparoscopy. For the group assigned medical treatment, MTX was administered on an outpatient basis and consisted of a course of four doses of 1mg/kg IM on d 0, 2, 4, and 6.

Outcome measures: Treatment success after 1° treatment, i.e. complete elimination of tubal pregnancy (serum β -hCG <2IU/L), tubal preservation rate after 1° treatment (i.e. need for salpingectomy), and tubal patency rates, based on HSG 3mo after completion of treatment.

Results

Table 26.2 Summary of results

| | MTX (n = 51) | Salpingostomy (n = 49) | |
|---|-----------------|---------------------------|------------------------------|
| 1° treatment success | 42 (82%) | 35 (72%) | RR (95% CI): 1.2 (0.93–1.4) |
| Median clearance time of β -hCG (d) | 19 | 14 | p = 0.64 |
| Tubal preservation | 46 (90%) | 45 (92%) | RR (95% CI): 0.98 (0.87–1.1) |
| Homolateral tubal patency | 23/37 (62%) | 23/35 (66%) | RR (95% CI): 0.95 (0.67–1.3) |

Discussion

In haemodynamically stable patients with unruptured tubal pregnancy, systemic MTX and laparoscopic salpingostomy were successful in treating the majority of cases. Persistent trophoblast occurred more commonly in the salpingostomy group, whereas more surgical re-interventions were required in the medically treated group. There was no significant difference between treatments in homolateral patency rates, after additional interventions were taken into account. The choice between the two treatment modalities was determined by patients' preferences and QoL. (See Table 26.2.)

Problems

- There was no limitation on the size of ectopic pregnancy or the initial serum β -hCG. However, the greater the size of the ectopic pregnancy and the higher the serum β -hCG concentration must have an adverse effect on clinical outcome, which was not addressed in this study.
- The study did not assess long-term fertility outcome.
- There was loss to F/U of patients having HSG to assess homolateral patency at 3mo.

Recurrent miscarriage and antiphospholipid antibodies

Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies).

AUTHORS: Rai R, Cohen H, Dave M *et al.*

REFERENCE: *BMJ* (1997) 314, 253–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This was one of the first RCTs to show that aspirin plus heparin therapy was superior to aspirin alone in managing recurrent miscarriage with antiphospholipid antibodies.

Impact

Use of a combination of LMWH and aspirin in recurrent miscarriage associated with antiphospholipid antibodies has become routine practice.

Aims

Prognosis for pregnancies in women with recurrent miscarriage and antiphospholipid antibodies is poor, with a 90% rate of fetal loss if no treatment is given during pregnancy. Several different treatments, such as aspirin, heparin, corticosteroids, and IgG, were used either alone or in combination, with little evidence on efficacy. This study aimed to determine whether aspirin and heparin leads to a higher rate of live births, compared to aspirin alone.

Methods

Patients: 90 women from one centre in the UK.

Inclusion criteria: Pregnant women with three or more consecutive miscarriages and positive antiphospholipid antibodies on at least two occasions >8wk apart before becoming pregnant.

Exclusion criteria: Women with previous thromboembolism, SLE, uterine abnormality, hypersecretion of luteinizing hormone (LH), multiple pregnancy, abnormal karyotype (in patient or partner).

Groups:

- Low-dose aspirin (75mg od) and UFH (5,000IU bd) until 34wk gestation ($n = 45$);
- Low-dose aspirin only until 34wk gestation ($n = 45$).

Outcome measures: Rate of live births and miscarriage.

Results

Table 26.3 Summary of results

| | Aspirin only (<i>n</i> = 45) | Aspirin and heparin (<i>n</i> = 45) | |
|---------------------|----------------------------------|---|-----------------|
| No. of live births | 19 (42%) | 32 (71%) | <i>p</i> = 0.01 |
| Loss of pregnancy | | | |
| Under 14wk | 24 | 11 | <i>p</i> = 0.59 |
| Between 14 and 28wk | 2 | 2 | <i>p</i> = 0.62 |

Discussion

This trial showed that treatment with low-dose aspirin and heparin leads to a significantly higher rate of live births than aspirin alone in women with recurrent miscarriages and antiphospholipid antibodies. Most miscarriages in the two groups occurred in the first trimester, which supports the view that the mechanism of recurrent miscarriage in such women is due to antiphospholipid antibodies inhibiting trophoblast invasion. Once placentation is established, their thrombogenic action causes decreased placental perfusion and infarction. (See Table 26.3.)

Problems

- This was a small study, and it did not compare the efficacy of LMWH and UFH in the prevention of recurrent miscarriage.

Unexplained recurrent miscarriage

ALIFE (**A**nticoagulant for **L**iving **F**etus): Aspirin plus heparin or aspirin alone in women with recurrent miscarriage.

AUTHORS: Kaandorp SP, Goddijn M, Van der Post JA et al.

REFERENCE: *N Engl J Med* (2010) 362, 1586–96.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Neither aspirin alone nor aspirin combined with LMWH improved the live birth rate in women with unexplained miscarriage.

Impact

Women with unexplained miscarriage have an excellent prognosis for future pregnancy outcome, without pharmacological input. Empirical treatment with anticoagulant therapy in women with unexplained miscarriages is unnecessary.

Aims

Recurrent miscarriage is defined as three or more consecutive miscarriages and affects 1% couples. There are various causes implicated in recurrent miscarriage and include uterine abnormalities, abnormal parental karyotype, and antiphospholipid syndrome. Even after thorough investigation, recurrent miscarriage remains unexplained in over 50% of cases. The use of aspirin and LMWH in women with recurrent miscarriages and antiphospholipid antibodies has become routine practice, but this treatment regime is increasingly being used to manage recurrent miscarriage where there is no identifiable cause. This study aimed to determine the effectiveness of the use of aspirin and heparin in women with unexplained recurrent miscarriage.

Methods

Patients: 364 women at seven centres in The Netherlands.

Inclusion criteria: Women with two or more recurrent miscarriages who were attempting to conceive or <6wk pregnant.

Exclusion criteria: Women with antiphospholipid antibodies, previous thromboembolism, uterine anomalies, abnormal karyotype.

Groups:

- Aspirin (80mg od) and LMWH (nadroparin 2,850 IU) ($n = 123$);
- Aspirin (80mg od) only ($n = 120$);
- Placebo ($n = 121$).

Primary outcome: Live birthweight.

Secondary outcomes: Miscarriage rate, obstetric complications, maternal/fetal adverse effects.

Results

Table 26.4 Summary of results

| ITT | Aspirin and LMWH (n = 123) | Aspirin (n = 120) | Placebo (n = 121) | |
|------------------------------|-------------------------------|----------------------|----------------------|------------|
| No. of live births | 54.5% | 50.8% | 57.0% | $p = 0.63$ |
| Women who became pregnant | Aspirin and LMWH (n = 99) | Aspirin (n = 97) | Placebo (n = 103) | |
| No. of live births | 69.1% | 61.6% | 67.0% | $p = 0.52$ |

Discussion

Neither aspirin nor aspirin in combination with LMWH, compared to placebo, improved the live birthweight in women with unexplained recurrent miscarriages, thus supporting the thinking that all unexplained miscarriages cannot be due to thrombosis. There was also an increased tendency of bruising, swelling, and itching at the injection site in the combination therapy group. (See Table 26.4.)

Problems

- The study was not powered to assess certain subgroups that might have had a different response. Only 16% of participants had an identified inherited thrombophilia, and it is possible that these women may have benefited from this therapy.

Prevention of preterm birth: cervical cerclage

Multicenter randomized trial of cerclage for preterm birth prevention in high-risk women with shortened midtrimester cervical length.

AUTHORS: Owen J, Hankins G, Iams JD *et al.*

REFERENCE: *Am J Obstet Gynecol* (2009) **201**, 375.e1–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There was a clear interaction between cervical length at randomization and cerclage effectiveness. In women with a prior spontaneous preterm delivery and cervical length <25wk, cerclage reduced mid-trimester miscarriage and perinatal mortality but did not prevent birth <35wk, unless cervical length >15mm.

Impact

The UK's RCOG *Green-top Guideline Cervical Cerclage 2011* recommends that women with a history of ≥ 1 spontaneous preterm birth or mid-trimester loss who are undergoing ultrasound cervical length screening should be offered an ultrasound-indicated cerclage if the cervix is <25mm long before 24wk.

Aims

Preterm birth before 37wk occurs in 7–8% of live births and is the leading cause of perinatal morbidity and mortality. The role of cervical cerclage was first performed in 1902 in women with prior mid-trimester loss or preterm birth which was thought to be due to 'cervical incompetence'. However, the use of cervical cerclage is controversial. It has been used by obstetricians as prophylaxis against preterm labour in women considered to be at high risk, e.g. multiple pregnancy, uterine anomalies, previous cone biopsy, ultrasound findings, without any clear evidence of benefit in a specific population. This study aimed to assess the effectiveness of cervical cerclage in preventing recurrent preterm birth in women with a short cervix.

Methods

Patients: 301 patients at 15 centres in the USA.

Inclusion criteria: Healthy multiparous women with singleton pregnancies with ≥ 1 prior spontaneous preterm birth or mid-trimester loss with cervical length on ultrasound <25mm prior to 22⁺6wk gestation.

Exclusion criteria: Fetal anomaly, planned history-indicated cerclage, clinically significant maternal/fetal complication, e.g. chronic HTN.

Groups:

- Cerclage ($n = 148$);
- No cerclage ($n = 153$).

Primary outcome: Birth <35wk gestation.

Secondary outcomes: Birth >7d after randomization, pre-viable birth <24wk, and perinatal death.

Results

Table 26.5 Summary of results

| | No cerclage (n = 153) | Cerclage (n = 148) | p |
|---------------------------|-----------------------|--------------------|-------|
| Primary outcome | | | |
| Birth <35wk | 32% | 42% | 0.09 |
| Secondary outcomes | | | |
| Pre-viable birth | 14% | 6.1% | 0.03 |
| Preterm birth <37wk | 60% | 45% | 0.01 |
| Perinatal death | 16% | 8.8% | 0.046 |

- Primary outcome: Although the benefit of cerclage at a cervical length of 25mm was not significant, in those with cervical length <15mm, there was a significant benefit from cerclage assignment ($p = 0.006$) (See Table 26.5.)

Discussion

Although there was not a statistically significant benefit of cerclage for the primary outcomes, there were clear benefits for secondary pregnancy outcomes. Furthermore, this study demonstrated that risk of prematurity was inversely proportional to cervical length. It showed a clear benefit of ultrasonographic assessment in women with a history of previous spontaneous preterm delivery, with effectiveness of cerclage when the cervical length is very short, i.e. <15mm.

Problems

- The study design limited screening and randomization at 22⁺⁶wk gestation, potentially missing those patients who may have continued to experience pathological cervical shortening after completion of ultrasound screening.

Pre-eclampsia: preventing seizures

MAGPIE (MAGnesium sulphate for the PreventIon of Eclampsia) trial:

Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate?

AUTHORS: Altman D, Carroli G, Duley F *et al.*

REFERENCE: *Lancet* (2002) **359**, 1877–90.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Magnesium sulfate halves the risk of women with pre-eclampsia developing seizures and also reduces the risk of maternal death, with no associated substantive SEs to mother or baby.

Impact

This trial clearly showed the effectiveness and safety of magnesium sulfate in the treatment and prevention of this serious disorder of pregnancy. As such, it has now become established as the treatment of choice for this condition

Aims

Hypertensive disorders of pregnancy are the second leading cause of maternal mortality. Pre-eclampsia is a multisystem disorder complicating 2–8% of pregnancies and can lead to eclampsia-superimposed convulsions. The mainstream treatment for severe pre-eclampsia has been the use of anticonvulsants (e.g. diazepam). Although magnesium sulfate has shown promising early results, its use has not been validated by robust clinical trials to prove its efficacy. This study aimed to confirm whether magnesium sulfate could reduce the risk of eclampsia and was safe for mother and baby.

Methods

Patients: 10,141 women at 33 international centres.

Inclusion criteria: Cases of pre-eclampsia in women who had not yet given birth or were ≤ 24 h post-partum, with:

- BP $\geq 140/90$ mmHg;
- Proteinuria $\geq 1+$.

Groups:

- Magnesium sulfate: ($n = 5,071$);
- Placebo ($n = 5,070$).

Protocol:

- IV: Loading dose of 8mL (4g of either magnesium sulfate or placebo) diluted with normal saline, given IV over 10–15min. Followed by IV maintenance infusion (over 24h) of 2mL/h (1g/h) of either agent;
- IM: Alternatively, IM injection used, with the same 8mL loading dose, and maintenance of 20mL of trial treatment given as 10mL (5mg of either agent) into each buttock, followed by 10mL (5g of either agent) every 4h for 24h.

Primary outcome: Eclampsia and (for women randomized before delivery) neonatal mortality rate.

Secondary outcome: Maternal morbidity.

Follow-up: Until discharge from hospital post-delivery.

Results

Table 26.6 Summary of results

| Primary outcomes | Magnesium sulfate (n = 5,055) | Placebo (n = 5,055) | RR (95% CI) |
|--------------------------|----------------------------------|------------------------|----------------------------|
| Eclampsia | 40 (0.8%) | 96 (1.9%) | 0.42 (0.29–0.60) |
| Maternal death | 11 (0.2%) | 20 (0.4%) | 0.55 (0.26–1.14) |
| Risk of baby dying | 576 (12.7%) | 558 (12.4%) | 1.02 (99% CI 0.92–1.14) |
| Secondary outcome | | | |
| Any serious morbidity | 196 (3.9%) | 183 (3.6%) | ns |

Discussion

This was, by far, the largest and most robust clinical trial conducted on hypertensive disease of pregnancy. It was a multinational study across a diverse population, involving a wide range of clinical settings in both rich and poor countries. The trial design was robust, as were the results. Compared to placebo, magnesium sulfate reduced the risk of eclampsia by 58%. Maternal mortality was lower in the magnesium sulfate group, but there was no clear difference between the groups in the risk of the baby dying. However, although maternal mortality was lower in the magnesium sulfate group, there was no clear difference between groups in any measure of serious maternal morbidity. (See Table 26.6.)

Problems

- Although the maternal mortality was lower in the magnesium group, the numbers were too small (11 vs 20) to draw firm conclusions. There were nine more deaths in the placebo group, but they were in the renal failure, embolism, and infection categories, which are unlikely to be affected by the administration of magnesium sulfate.

Follow-up

- The Magpie Trial Follow-up Study Collaborative group showed that magnesium sulfate prophylaxis was not associated with an excess of death or disability of women after 2y, or in an increase in death or disability for children at 18mo, hence confirming the safety of magnesium sulfate.

Preterm rupture of membranes and spontaneous labour: antibiotics

ORACLE (Overview of the Role of Antibiotics in Curtailing Labour and Early delivery): Broad-spectrum antibiotics for preterm, prelabour rupture of fetal membranes (Arm 1) and spontaneous preterm labour (Arm 2).

AUTHORS: Kenyon S, Taylor D, Tarnow-Mordi W (ORACLE Group).

REFERENCE: *Lancet* (2001) 357, 979–88 (Arm 1) and 989–94 (Arm 2).

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Arm 1 (A1): routine erythromycin use in preterm, prelabour rupture of membranes (pPROM) is associated with improved neonatal outcome. Co-amoxiclav (either alone or in combination with erythromycin) should not be used in pPROM, as it is associated with a higher incidence of neonatal necrotizing enterocolitis. Arm 2 (A2): antibiotics should not be routinely prescribed in spontaneous preterm labour (SPL) when there is no evidence of clinical infection.

Impact

The recommendations of this trial have, in particular, influenced the management of pPROM by introducing routine use of erythromycin.

Aims

Preterm delivery accounts for 75–80% of all neonatal morbidity and mortality; 30–40% of cases involve pPROM. There is uncertainty about the role of infection (especially subclinical) in preterm labour, and, although used, there had been uncertainty regarding the true efficacy of prophylactic antibiotics in both SPL with intact membranes and pPROM. This study was designed to compare routine use of erythromycin, co-amoxiclav, or both, in women with pPROM (A1) and SPL with intact membranes (A2).

Methods

Patients: 4,809 (A1)/6,295 (A2) women at 161 international centres.

Inclusion criteria:

- A1: Patients with pPROM, <37wk gestation;
- A2: Suspected/definite SPL with intact membranes, <37wk gestation.

Exclusion criteria: Already on/predicted need for antibiotics.

Groups:

- Erythromycin (250mg) and co-amoxiclav (325mg) ($n = 1,192$ A1; 1,565 A2);
- Erythromycin only ($n = 1,197$ A1; 1,611 A2);
- Co-amoxiclav only ($n = 1,212$ A1; 1,550 A2);
- Placebo ($n = 1,225$ A1; 1,569 A2).

Primary outcome: Composite of death before discharge, O_2 need at 36wk post-natal gestational age, and major cerebral abnormality on USS.

Secondary outcomes:

- A1: Delivery <37wk; gestation and weight at birth; respiratory distress syndrome (RDS); surfactant use; neonatal infection/necrotizing enterocolitis (NEC); time on O₂, the ventilator, and in hospital;
- A2: Delivery within 48h/1wk; mode of delivery; days in hospital; maternal antibiotic use post-delivery/pre-discharge; gestation and weight at birth; admission to NICU or special care baby unit.

Results

- A1 primary composite outcome (see Table 26.7);
- A1 secondary outcomes (erythromycin): Significant decrease in surfactant use (12.8% vs 16.3%, $p = 0.02$);
- A2 primary composite outcome (see Table 26.8).

Table 26.7 Summary of results

| | Erythromycin | Placebo | <i>p</i> |
|-------------|-------------------|-------------------|----------|
| All infants | 151/1,190 (12.7%) | 186/1,225 (15.2%) | 0.08 |
| Singletons | 125/1,111 (11.2%) | 166/1,149 (14.4%) | 0.02 |

Table 26.8 Summary of results

| Erythromycin | Co-amoxiclav | Both | Placebo |
|--------------|--------------|-----------|-----------|
| 90 (5.6%) | 76 (5.0%) | 91 (5.9%) | 78 (5.0%) |

Discussion

A1: Significantly fewer in the erythromycin group (singleton pregnancies) had primary composite outcomes. Erythromycin also associated with prolongation of pregnancy and reduction in surfactant use. Although co-amoxiclav was associated with prolongation of pregnancy, it was also associated with significant rise in neonatal NEC.

A2: No antibiotics associated with lower rates of primary composite outcome, and none with prolonged pregnancy, influenced delivery mode, or length of stay.

Problems

- As antibiotics did not decrease the rates of primary composite outcome, the authors concluded that the role of subclinical infection in premature birth might have been overestimated. However, as the trial did not report assessments of amniotic fluid/placenta microbiology or inflammatory markers, this conclusion may be inappropriate.

Follow-up

Oracle Children's Study (Kenyon *et al.* *BMC Pregnancy and Childbirth* (2008) 8, 14): followed up children to 7y. pPROM: maternal antibiotics made no difference to function, behaviour, key stage 1 results. Small increase in non-serious bowel problems with co-amoxiclav (e.g. constipation). SPL (intact membranes): the erythromycin group had more mild 'functioning' problems (42% vs 38%). Cerebral palsy commoner, following antibiotics (4.4% vs 1.7%). Summary: erythromycin can have only short-term benefits for children, following pPROM. No benefit in antibiotics for SPL with intact membranes.

Prelabour rupture of membranes: management at term

TERMPROM trial: Induction of labour compared with expectant management for prelabour rupture of the membranes at term.

AUTHORS: Hannah M, Ohlsson A, Farine D et al.

REFERENCE: *N Engl J Med* (1996) 334, 1005–10.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Women with prelabour rupture of membranes (PROM) at term have similar outcomes with both active (induction of labour) and expectant management. Neonatal infection and Caesarean section (CS) rates are comparable in both groups. IV oxytocin is associated with lower maternal infection rates, and women prefer induction of labour.

Impact

With comparable outcomes between groups for this common condition, this trial has reassured clinicians and patients alike that they can together decide on a management option best suited to their needs and the capabilities of local service provisions. The results of this trial have been incorporated in protocols and guidelines worldwide.

Aims

PROM affects ~8–10% of all pregnancies; 90% of these women will spontaneously start labour within 24h. The risk of neonatal infection is a major concern with prolonged rupture of membranes. Although the risk is thought to be small in the first 24h, it increases thereafter. On the other hand, a premature intervention may increase the risk of unnecessary CS. Therefore, there remained no agreement as to whether early induction of labour or expectant management should be used. This trial was designed to assess and compare the available management options.

Methods

Patients: 5,041 women at 72 international centres.

Inclusion criteria:

- Women with PROM at term;
- ≥ 37 wk gestation;
- Single fetus in cephalic presentation.

Groups:

- Labour induced immediately with:
 - IV oxytocin ($n = 1,258$);
 - Prostaglandin E2 gel ($n = 1259$);

- Expectant management for up to 4d (in absence of complications). Labour induced with either:
 - Oxytocin ($n = 1263$); or
 - Prostaglandin E2 gel ($n = 1261$).

Primary outcome: Neonatal infection.

Secondary outcomes:

- The need for CS;
- Other measures of maternal, fetal, and neonatal health;
- Patient evaluation of the care they received.

Results

Table 26.9 Summary of results

| | Induction | | Expectant | |
|----------------------------|-----------------------------|----------------------------------|---------------------------------|----------------------------------|
| | Oxytocin ($n = 1,258$) | Prostaglandin ($n = 1,263$) | Oxytocin ($n = 1,259$) | Prostaglandin ($n = 1,261$) |
| Rate of neonatal infection | 2% | 3% | 2.8%; OR 0.7; 95% CI 0.4–1.2 | 2.7%; OR 1.7; 95% CI 0.1–1.8 |
| Rate of CS | 10.1% | 9.6% | 9.7%; OR 1.0; 95% CI 0.8–1.4 | 10.9%; OR 0.9; 95% CI 0.7–1.1 |

OR, odds ratio; OR/95% CI = vs same group who underwent induction.

Discussion

Both immediate induction of labour with Syntocinon® (oxytocin) or prostaglandins and expectant management of up to 96h with induction of labour in the presence of any complications (signs of fetal or maternal infection) had similar primary and secondary outcomes, i.e. similar rates of CS and neonatal infection. There was, however, a significantly lower risk of chorioamnionitis in the induction with the oxytocin group. These results had differing implications for different stakeholders. Some saw this as a vindication for conservative management, while others saw it as an opportunity to use prostaglandins. It also introduced the important element of informed patient choice. Maternal wishes should be taken into account when managing PROM. In this trial, immediate induction of labour with Syntocinon® was considered the 'best' option by the authors, with comparable CS rates and the lowest rates of clinical chorioamnionitis. This was also the patients' preferred choice. (See Table 26.9.)

Problems

- Although the authors concluded that oxytocin led to fewer infections and was preferred by patients, in practice, the difference in service provisions and resources between different countries and hospitals should be taken into account in the decision-making process; this was not discussed by the authors.

Breech presentation: mode of delivery

Term breech trial: Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial.

AUTHORS: Hannah M, Hannah W, Hewson S et al.

REFERENCE: *Lancet* (2000) **356**, 1375–83.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

For breech presentation at term, planned CS is safer for the fetus than planned vaginal delivery. Maternal complications are similar in both groups.

Impact

This trial has finally tipped the balance in favour of CS, having provided evidence that it is the safer option.

Aims

Breech presentation affects 3–4% of pregnancies at term. In recent years, vaginal breech deliveries in the Western world have been dramatically falling, mainly due to the fear of litigation. The evidence to date has been inconclusive, supporting neither planned CS nor vaginal birth. However, previous trials were small and possibly skewed, due to poor outcomes in premature babies in whom breech is more prevalent. Some studies were also biased, because women were not randomly allocated to different groups. This large RCT for breech at term aimed to resolve this contentious issue.

Methods

Patients: 2,088 women at 121 international centres (26 countries).

Inclusion criteria: Women with a singleton live fetus in a frank or complete breech presentation at term.

Exclusion criteria: Evidence of feto-pelvic disproportion, fetus clinically large or with an estimated weight of $\geq 4,000$ g, presence of hyperextension of the fetal head, contraindication to either labour or vaginal delivery.

Groups:

- Planned CS (section scheduled for ≥ 38 wk gestation) ($n = 1,043$);
- Planned vaginal birth (attended by experienced clinicians) ($n = 1,045$).

Primary outcomes: Perinatal or neonatal mortality at ≤ 28 d of age and serious neonatal morbidity.

Secondary outcomes: Maternal mortality or serious maternal morbidity during the first 6wk post-partum.

Follow-up: Mothers and babies had F/U to 6wk post-partum; 3mo and 2y F/U performed in selected centres.

Results

Table 26.10 Summary of results

| Primary outcome | Caesarean (n = 1,039) | Vaginal birth (n = 1,039) | RR and p |
|--|--------------------------|------------------------------|-----------------------|
| Perinatal and neonatal mortality, and serious neonatal morbidity | 17/ 1,039(1.6%) | 52/1,039(5.0%) | RR 0.33; p <0.0001 |
| Secondary outcome | | | |
| Maternal mortality or serious maternal morbidity | 41/ 1,041(3.9%) | 33/1,042(3.2%) | RR 1.24; p <0.4 |

Discussion

The ideal management of breech fetus at term had previously been controversial. In the absence of robust RCT data, clinicians had been guided by medico-legal concerns, data from non-randomized trials, and personal preferences. This trial showed that the perinatal and neonatal mortality, as well as serious neonatal morbidity, was three times lower if delivery was by elective CS, as compared with vaginal delivery. (See Table 26.10.)

Problems

- Inclusion criteria were not always strictly adhered to, and some candidates were not suitable for vaginal breech delivery (e.g. a fetus with a large meningomyelocele).
- Some centres lacked adequate diagnostic resources. Hyperextension of the fetal neck is a contraindication for vaginal breech delivery, but, in one-third of cases assigned to the vaginal delivery group, an ultrasound scan was not performed to check for this condition.
- A subsequent 2y F/U of toddlers (in selected centres) did not show significant differences in outcome between the two techniques.
- A number of cases with neonatal mortality or morbidity were attended during labour by an unskilled practitioner. Although this may indicate flaws in executing the trial methodology, it also represents the reality in most hospitals today—clinicians skilled in the art of vaginal breech delivery have become a rarity.
- Subsequent studies in carefully selected populations of breech presentation at term (the largest being the PREMODA study group in France and Belgium, 2006) showed comparable outcomes with planned vaginal delivery and planned CS, when strict selection criteria were used, e.g. normal pelvimetry, no hyperextension of the fetal head, estimated weight of 2.5–3.8kg, frank breech, and continuous FH monitoring).
- However, further subanalyses of this trial showed that, even after excluding cases of breech delivery with prolonged labour, induced/augmented labours, footling breeches, and lack of skilled operators, there was still an increased risk of neonatal morbidity/mortality vs planned CS (1.6% vs 3.35%, $p = 0.02$). This remains the largest RCT with useful results for all practitioners in both the developed and developing world.

Hormone replacement therapy

WHI (Women's Health Initiative) study: Risks and benefits of estrogen plus progestin in healthy postmenopausal women.

AUTHORS: Rossouw J, Anderson G, Prentice R et al.

REFERENCE: JAMA (2002) 288, 321–33.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First trial to directly demonstrate that HRT carries an increased risk of CHD, stroke, breast cancer, and venous thrombosis.

Impact

The initial reaction to the results of the WHI study was to recommend that HRT should be prescribed 'in the lowest dose for the shortest possible time' in women with severe menopausal symptoms (after fully informing them of the added risks). Following 2° analyses, the British Menopause Society had advised that the decision for HRT is an individual decision and, when prescribed before the age of 60, has a favourable benefit/risk profile. In fact, women with early menopause should be encouraged to start HRT, until at least the average age of menopause. If used over the age of 60, lower doses should be used, preferably via the transdermal route.

Aims

The WHI study included both RCT and observational elements. While the latter looked at the impact of lifestyle factors on health outcomes, the RCT component was divided into three arms. This arm aimed to evaluate the benefits and risks associated with HRT in post-menopausal women with an intact uterus. The other two arms evaluated: (1) the effects of dietary modification on breast/colorectal cancer and CV risk and (2) the effect of calcium and vitamin D supplementation on osteoporotic fracture and colorectal cancer risk.

Methods

Patients: 16,608 women from 40 centres in the USA.

Inclusion criteria: Age 50–79y; Post-menopausal (defined as no vaginal bleeding for 6mo (12mo if age 50–54y), or a history of previous post-menopausal hormone therapy use); uterus still present.

- **Exclusion criteria:** Any medical condition likely to cause predicted survival <3y; prior breast/other cancer (in past 10y), except non-melanoma skin cancer; low haematocrit or platelet count; poor compliance.

Groups:

- Oestrogen (conjugated equine oestrogen 0.625mg/d) and progesterone (medroxyprogesterone acetate 2.5mg/d) ($n = 8,506$);
- Placebo ($n = 8,102$).

Primary endpoints: CHD, includes non-fatal MI and CHD deaths, and need for CABG or PTCA, invasive breast cancer.

Secondary endpoints: Fractures, other CV disease not in primary endpoint, and endometrial, colorectal, and other cancers.

Follow-up: Symptom review at 6wk, then every 6mo thereafter. F/U stopped after 5.2y (intended to be 8.5y).

Results

Table 26.11 Summary of results

| Primary endpoint | HRT (n = 8,506) | Placebo (n = 8,102) | HR | Nominal 95% CI |
|-------------------------------|--------------------|------------------------|------|-------------------|
| CHD | 164 | 122 | 1.29 | 1.02–1.63 |
| Invasive breast cancer | 166 | 124 | 1.26 | 1.00–1.59 |
| Secondary endpoints | | | | |
| Stroke | 127 | 85 | 1.41 | 1.07–1.85 |
| Venous thromboembolic disease | 151 | 67 | 2.11 | 1.58–2.82 |
| Endometrial cancer | 22 | 25 | 0.83 | 0.47–1.47 |
| Colorectal cancer | 45 | 67 | 0.63 | 0.43–0.92 |
| Hip fractures | 44 | 62 | 0.66 | 0.45–0.98 |

Discussion

This trial was stopped early, as women with a uterus who were taking the combined oestrogen and progesterone HRT were found to have an excessive risk of breast cancer. Therefore, it was felt the health risks associated with treatment exceeded the health benefits. At the time of stopping, the risks of CHD, stroke, PE, and invasive breast cancer were significantly increased in the HRT group. There were smaller reductions in the numbers of hip fractures and colorectal cancers. (See Table 26.11.)

Problems

- Only one dose investigated, so risks may differ with lower doses or other routes of administration.
- The majority of participants were >10y past the menopause.
- The study did not include patients who had prior hysterectomy.
- The reduction in fracture risk or incidence of colorectal cancer may have been underestimated, due to early trial termination.
- Relative, rather than absolute, risks were reported.

Follow-up

- 2° analysis of the WHI study (Rossouw *et al.* *JAMA* (2007) 297, 1465–77) showed that younger women (50–59y old) taking HRT over a 10y period have no increased risk of CVD, while the WISDOM study (Vickers *et al.* *BMJ* 2007) showed that women starting or restarting HRT many years after the menopause had increased CV risk.
- The absolute risk of breast cancer is small and appear to be linked to the duration of HRT. It has also been shown that the risk of breast cancer can be reduced by stopping HRT (Chlebowski *et al.* *N Engl J Med* 2009).

Polycystic ovary syndrome: metformin treatment

Ovarian function and metabolic factors in women with oligomenorrhea treated with metformin in a randomized double blind placebo-controlled trial.

AUTHORS: Fleming R, Hopkinson Z, Wallace A et al.

REFERENCE: *J Clin Endocrinol Metab* (2002) **87**, 569–74.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Metformin therapy improves ovulation in oligomenorrhoeic women with polycystic ovaries.

Impact

Metformin treatment is routinely used in women with PCOS.

Aims

The role of insulin resistance in the aetiology of PCOS is well recognized, as is the link with the metabolic syndrome. This RCT aimed to confirm anecdotal evidence for the benefit of oral hypoglycaemics in PCOS.

Methods

Patients: 94 patients (two withdrew before treatment) at one centre in the UK.

Inclusion criteria:

- Aged <35y;
- Women with oligomenorrhoea (cycle length >41d; <8 cycles/y) or amenorrhoea and polycystic ovaries.

Exclusion criteria:

- Significant hyperprolactinaemia;
- Abnormal thyroid function tests;
- Congenital adrenal hyperplasia.

Groups:

- Metformin ($n = 45$);
- Placebo ($n = 47$).

Endpoints:

- Ovarian function;
- Anthropometric criteria;
- Glycaemic indices;
- Leptin;
- Lipid profile.

Follow-up: At 14wk after treatment (between 12 and 16wk).

Results

Table 26.12 Summary of results

| Endpoint | Metformin (n = 45) | Placebo (n = 47) | p |
|---|--------------------|------------------|--------|
| Ovulation frequency | 23% | 13% | <0.01 |
| Day to first ovulation (d) | 23.6 | 41.8 | 0.02 |
| Failed to ovulate | 8 | 17 | 0.04 |
| Luteal ratio | 23% | 13% | <0.001 |
| Luteal phases with progesterone concentration <7ng/mL | 2 (8%) | 5 (13%) | ns |
| Dropout rate | 15% | 5% | <0.05 |

Table 26.13 Summary of results

| Change from baseline | Metformin | Placebo |
|----------------------------|-----------|---------|
| BMI (SD) | -0.6* | 0.3* |
| Waist/hip ratio | 0 | 0 |
| Leptin (ng/mL) | -3.8 | -2.1 |
| Fasting insulin (mIU/L) | -0.4 | -0.9 |
| Fasting glucose (nmol/L) | 0 | 0.1 |
| Total cholesterol (nmol/L) | -0.11 | -0.03 |
| Triglycerides (mmol/L) | 0.01 | 0.04 |
| VLDL (mmol/L) | 0.02 | 0.12 |
| LDL (mmol/L) | -0.2 | -0.14 |
| HDL (mmol/L) | 0.06* | 0 |

HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

* p < 0.05; all other values = ns.

- Ovarian function and dropout rate (see Table 26.12).
- Metabolic parameters (see Table 26.13).

Discussion

This study showed a significant, but modest, benefit of metformin treatment on ovarian function, as well as anthropometric and HDL lipid measurements, in patients with PCOS. The increase in the ovulation rate occurred much more rapidly with metformin. However, there were no changes in androgen concentrations, glucose, insulin, triglyceride, or very low-density lipoprotein (VLDL) levels. Subgroup analysis suggested that the least androgenic patients were more likely to respond to metformin treatment.

Problems

- There was a high (significant) dropout rate in the metformin group (>30%), mainly due to GI SEs; this compliance issue has important clinical relevance.
- The effect of different metformin doses on ovarian and metabolic function was not analysed.

Polycystic ovary syndrome: infertility treatment

Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome.

AUTHORS: Legro R, Barnhart H, Schlaff W *et al.*

REFERENCE: *N Engl J Med* (2007) **356**, 551–66.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Clomiphene is more effective than metformin for the treatment of PCOS-related infertility.

Impact

Clomiphene is considered the best first-line treatment for infertility in patients with PCOS.

Aims

PCOS is the commonest reproductive endocrinopathy and represents a major cause of subfertility. This study aimed to determine whether clomiphene, metformin, or a combination of the two therapies would result in the highest birth rate in patients with PCOS-related infertility.

Methods

Patients: 626 patients from multiple centres in the USA.

Inclusion criteria:

- History of oligomenorrhoea (no more than 8 menses/y);
- Hyperandrogenaemia.

Exclusion criteria:

- Hyperprolactinaemia;
- Congenital adrenal hyperplasia;
- Thyroid disease;
- Amenorrhoea not related to PCOS;
- Clinically suspected Cushing's syndrome;
- Androgen-secreting neoplasm.

Groups:

- CL: Clomiphene ($n = 209$);
- M: Metformin ($n = 208$);
- C: Combination of metformin and clomiphene ($n = 209$).

Primary endpoints: Rate of live births.

Secondary endpoints:

- Rate of pregnancy loss;
- Singleton birth;
- Ovulation;
- Adverse events.

Follow-up: Up to 6mo.

Results

Table 26.14 Summary of results

| Endpoint (% of patients) | CL | M | C | p | | |
|---------------------------------------|------|------|------|--------|---------|---------|
| | | | | C vs M | C vs CL | CL vs M |
| Live births | 22.5 | 7.2 | 26.8 | <0.001 | 0.3 | <0.001 |
| Ovulation | 49.0 | 29.0 | 60.4 | <0.001 | 0.003 | <0.001 |
| Singleton pregnancies | 94.0 | 100 | 96.9 | 1.0 | 0.5 | 1.0 |
| First trimester pregnancy loss | 22.6 | 40 | 25 | 0.2 | 0.7 | 0.1 |
| Conception rate in those who ovulated | 39.5 | 21.7 | 46 | <0.001 | 0.2 | 0.002 |
| Serious adverse events | 3.3 | 1.0 | 5.3 | 0.02 | >0.05 | 0.1 |

C, combination; CL, clomiphene; M, metformin.

Discussion

PCOS is a major cause of infertility. Metformin had been used in recent years as first-line therapy, though data for its use had mainly been derived from small studies. This study demonstrated that conception, pregnancy, live births, and multiple births were significantly more likely to occur with clomiphene, rather than metformin, therapy. Despite clomiphene being more effective than metformin, only just over 20% of women gave birth. Compared with single-agent treatment, ♀ treated with combination therapy had higher ovulation rates, but this did not translate into higher pregnancy or live birth rates. Pregnancy-related adverse events were commoner in the clomiphene and combination groups. (See Table 26.14.)

Problems

- There was a high dropout rate of 23.4–34.6% in the three groups, with the metformin group having a significantly higher dropout rate.
- Extended slow-release metformin was used, instead of the commoner immediate-release metformin. This may have contributed to the lower efficacy of metformin seen in this study.

Uterine fibroids: embolization vs surgery

REST (**R**andomised trial of **E**mbolization vs **S**urgical **T**reatment): Uterine-artery embolization versus surgery for symptomatic uterine fibroids.

AUTHORS: Edwards R, Moss J, Lumsden M *et al.* (Committee of the Randomized Trial of Embolization versus Surgical Treatment for Fibroids).

REFERENCE: *N Engl J Med* (2007) **356**, 360–70.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In women with symptomatic fibroids, the lower cost and faster recovery after embolization must be weighed against the need for further treatment in a minority. Surgery offered better long-term symptom control, but QoL was similar at 1y.

Impact

These findings have helped clarify the treatment options for uterine fibroids.

Aims

Uterine fibroids are the commonest ♀ reproductive tract tumour, associated with menstrual disorders, subfertility, miscarriage, and pressure effects. Uterine artery embolization, a uterus-sparing and less invasive procedure, has become increasingly popular (*Radiology* (2003) **226**, 425–31). This study aimed to compare uterine artery embolization with surgery (hysterectomy/myomectomy).

Methods

Patients: 157 patients at 27 centres in the UK.

Inclusion criteria:

- Age >18y with ≥1 fibroid (>2cm in diameter) visible on MRI;
- Symptoms (menorrhagia/pelvic pain/pressure) warranting surgery.

Exclusion criteria:

- Pregnancy/severe contrast allergy/other contraindication to MRI/surgery;
- Subserosal pedunculated fibroids;
- Recent or ongoing PID.

Groups: Randomized in a 2:1 ratio:

- Embolization (*n* = 106);
- Surgery (*n* = 51).

Primary endpoint: QoL at 1y assessed using Medical Outcomes Study SF36 item general health questionnaire.

Secondary endpoints: EuroQol-5D questionnaire to measure preferences for certain health outcomes, time until resumption of usual activities, recommendation to friend, 24h pain score, complications, and treatment failure (i.e. needed later hysterectomy/repeat embolization).

Follow-up: Outcomes at 1, 6, 12, and 21mo; then annual F/U.

Results

- Symptoms: No significant differences in QoL at 1y. The embolization group had less time before resuming all usual activities ($p < 0.001$). (See Table 26.15.)

Table 26.15 Summary of results

| | Embolization (n = 95) | Surgery (n = 45) | p |
|--|--|-------------------------------------|------------|
| Symptom score (1mo) | 1.5 (\pm 2.4) | 2.8 (\pm 2.6) | 0.004 |
| Symptom score (12mo) | 3.6 (\pm 2.0) | 4.3 (\pm 11.7) | 0.03 |
| Pain score (24h) | 3.0 (\pm 2.1) | 4.6 (\pm 2.3) | <0.001 |
| Hospital stay | 1d | 5d | <0.001 |
| Minor complications | 36 (34%) (mostly post-embolization syndrome) | 10 (20%) (mostly minor infections) | 0.06 |
| Major adverse events (at 1y) | 13 (12%) | 10 (20%) | 0.2 |
| Treatment failures (required additional procedure) | 21 (20%) (10 (9%) during first year) | 1 (2%) (myomectomy to hysterectomy) | Not stated |
| Mean cost saving | UK £951 (at 1y) | — | — |

Discussion

Neither treatment was perfect, both having pros and cons. Although QoL at 1y was equal, symptom control was better with surgery. However, embolization was cheaper, with faster recovery and resumption of usual activities. The rate of complications did not differ significantly, but timing did—the surgical group's occurred largely during the hospital stay, while the embolization group's occurred post-discharge. The major disadvantage of embolization was that 20% required further treatment for recurrence or persistence of symptoms, half within the first year.

Problems

- No standardization of the technique for either procedure (two types were used).
- Primary outcome (SF36) related to QoL, and was not related to fibroid-specific symptoms.
- 'Time until resumption of usual activities' is open to bias, as patients may expect to take longer to recover from surgery.

Ophthalmology

Introduction 738

Glaucoma: control of intraocular pressure 740

Glaucoma: medical vs surgical treatment 742

Glaucoma: topical medication 744

Glaucoma: early treatment 746

Age-related macular degeneration: vascular endothelial growth factor antagonists 748

Age-related macular degeneration: ranibizumab and bevacizumab for treatment of neovascularization 750

Diabetic retinopathy: laser photocoagulation 752

Diabetic retinopathy: photocoagulation for macular oedema 754

Diabetic retinopathy: laser and vascular endothelial growth factor antagonists for macular oedema 756

Retinal vein occlusion: intravitreal dexamethasone implant for macular oedema 758

Myopia: surgical correction 760

Ocular herpes simplex: antiviral treatment 762

Introduction

The commonest cause of treatable visual disability in the world is cataract. Historically, cataracts were removed (if they were removed at all) by an extremely unsatisfactory procedure called 'couching', an operation entailing puncture of the eye with a needle and an attempt to push the cloudy lens out of its normal location with the needle tip. The ultimate goal was to dislodge the lens and remove it away from the patient's visual axis. Not only was this procedure excruciatingly painful, but the visual results were often disastrous. These days, small incisional surgery is undertaken using phacoemulsification and implantation of an intraocular lens under local anaesthesia, resulting in a rapid, and often spectacular, improvement in vision. Justifiably, the operation is considered one of the most rewarding in all of medicine. However, it took many years of slow progress to develop the technique that is now used. The first intraocular lens implant was inserted by Sir Harold Ridley in 1949 and was met with opposition from the medical community. It took three decades of struggle, before the procedure was undertaken routinely. Dr Charles Kelman first undertook small incisional surgery, using phacoemulsification and aspiration of the cataract, in 1967. Once again, it took almost two decades for this technique to be adopted. It could be argued that the reason for the slow progress in this field was the fact that randomized studies comparing these new techniques with established practice were not undertaken at an early stage. In recent years, ophthalmologists have realized the importance of evidence-based studies of therapy in the other common causes of visual disability: diabetic retinopathy, chronic glaucoma, age-related macular degeneration (AMD), and the surgical treatment of myopia. The rapid acceptance of new therapy for these conditions has been a direct consequence of prospective RCTs. In this chapter, the most important studies in these fields will be considered.



Glaucoma: control of intraocular pressure

AGIS-7 (Advanced Glaucoma Intervention Study): The relationship between control of intraocular pressure and visual field deterioration.

AUTHORS: The AGIS Investigators.

REFERENCE: *Am J Ophthalmol* (2000) **130**, 429–40.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Consistently low intraocular pressure (IOP) measurements are associated with reduced progression of visual field (VF) defects in patients with advanced glaucoma.

Impact

Both a low average IOP (of <14mmHg) and an IOP consistently below 18mmHg lead to a dramatic slowing of VF loss in patients with glaucoma. This study gives clinicians a target IOP to aim for in the management of glaucoma.

Aims

Previous studies had suggested a correlation between low IOP and reduced glaucoma progression. This study compared two regimens of surgical intervention in patients with glaucoma and poorly controlled IOP on maximally tolerated medical therapy. By aiming to keep IOP <18mmHg, this study aimed to assess the effect of both a low average IOP and an IOP consistently <18mmHg on the progression of VF defects. This study was one of a series designed to provide a comprehensive overview of interventions for glaucoma.

Methods

Patients: 591 patients (789 eyes) at 11 centres across the USA.

Inclusion criteria:

- Age 35–80y;
- Open-angle glaucoma (defined by raised IOP, glaucomatous VF defect, and optic disc rim changes, uncontrolled by maximal topical medication);
- Phakic (eye containing a natural lens);
- Visual acuity (VA) better than 20/80;
- Both eyes enrolled, only if simultaneously eligible.

Groups: Randomized to receive one of two sequences of surgical intervention:

- 1: Argon laser trabeculoplasty, trabeculectomy, trabeculectomy;
- 2: Trabeculectomy, argon laser trabeculoplasty, trabeculectomy.

Topical medication used, as required, after each intervention (up to a maximum combination), aiming for an IOP <18mmHg.

Primary endpoint: VF deterioration (measured by change in VF score, with a positive score indicating deterioration).

Analysis: Two methods used: predictive analysis (PA) and associative analysis (AA). PA patients divided into three groups, depending on IOP level during the first 18mo. AA patients divided into four groups, based on the percentage of visits with IOPs <18mmHg.

Follow-up: Initial F/U at 3mo, then every 6mo for the duration of the study (range 4–7y).

Results

- At 8mo:

Table 27.1 Summary of results

| IOP over first 18mo | Change in VF score, compared to lowest IOP group | <i>p</i> |
|-----------------------|--|----------|
| <14mmHg (group A) | – | – |
| 14–17.5mmHg (group B) | 0.76 | 0.01 |
| >17mmHg (group C) | 1.89 | <0.001 |

Table 27.2 Summary of results

| Percentage of visits IOP<18mmHg | Change in VF score compared to group A | <i>p</i> |
|---------------------------------|--|----------|
| 100% (group A) | – | – |
| 75% (group B) | 1.11 | 0.02 |
| 50% (group C) | 1.97 | <0.001 |
| 25% (group D) | 2.42 | <0.001 |

Discussion

Both methods of analysis concluded that consistently low IOP slowed glaucoma progression (as measured by VF changes). IOP-lowering effects were greatest in group 1. Afro-American patients did better with initial laser trabeculoplasty, whereas Caucasians did better with initial trabeculectomy. Overall risk of cataract was 78%, with increased risk after the first trabeculectomy. In the lowest pressure group, some patients continued to progress, despite low IOP. (See Tables 27.1 and 27.2.)

Problems

- Only one VF used as a baseline for each patient.
- Despite the title, the study included some patients with early glaucoma and excluded very advanced glaucoma.
- Disease staging was not attempted.

Glaucoma: medical vs surgical treatment

CIGTS (Collaborative Initial Glaucoma Treatment Study): Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medications or surgery.

AUTHORS: Lichter P, Musch D, Gillespie B *et al.*

REFERENCE: *Ophthalmology* (2001) **108**, 1943–53.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Either medical or surgical treatment of newly diagnosed glaucoma result in a similar degree of VF loss and a similar VA after 5y. The IOP-lowering effect of surgery is greater.

Impact

Initial medical therapy, which carries fewer risks than surgery, is a valid option for 1° treatment of newly diagnosed glaucoma.

Aims

VF loss, and the subsequent blindness associated with open-angle glaucoma, is often preventable, if treated early. Initial studies had suggested that filtration surgery might be more efficacious than medical management (topical drops) for newly diagnosed disease. This study aimed to compare the outcome of 1° surgical treatment with that of medical treatment in patients with newly diagnosed glaucoma.

Methods

Patients: 607 patients at 14 clinical centres across the USA.

Inclusion criteria:

- Age 25–75y;
- Best corrected VA better than 20/40 in both eyes;
- Newly diagnosed open-angle glaucoma (including 1°, pigmentary, and pseudoexfoliative);
- One of:
 - IOP ≥ 20 mmHg and loss of three contiguous points on Humphrey visual field (HVF) and glaucomatous disc;
 - IOP 20–26mmHg and loss of two contiguous points on HVF;
 - IOP ≥ 27 mmHg and suspected glaucomatous disc.
- No prior ocular surgery, and no or limited prior topical treatment.

Groups: Both groups treated aggressively with a stepwise progression of treatments for pressure above target:

- Primary trabeculectomy (initially immediate procedure, proceeding to argon laser procedure, if failure; with or without 5-FU at the surgeon's discretion) ($n = 300$);
- Topical medication (usually commencing with a β -blocker) ($n = 307$).

Primary endpoint: VF loss.

Secondary endpoints:

- VA;
- IOP;
- Cataract.

Follow-up: 4–5y.

Results

Table 27.3 Summary of results

| Primary endpoint | Surgical group | Medical group | <i>p</i> |
|--|----------------|---------------|------------|
| Clinically significant VF loss | 13.5% | 10.7% | Not stated |
| Secondary endpoints | | | |
| Clinically substantial VA loss at some point over 5y | 7.2% | 3.9% | Not stated |
| Average IOP | 14–15mmHg | 17–18mmHg | 0.0001 |
| Cataract surgery | 17.3% | 6.2% | 0.0001 |

Discussion

Both baseline VF score and initial post-operative VA were worse in the surgical group than the medical group, but this difference was not sustained at 5y. The surgical group maintained a lower IOP (by about 3mmHg) throughout the study but had a higher rate of cataract formation. (See Table 27.3.)

Problems

- Inclusion criteria may have allowed recruitment of some patients with ocular HTN (OHT) who had less risk of progression than those with early glaucoma.
- In the surgical group, initial trabeculectomy was sometimes augmented with 5-FU, which may affect outcomes.
- F/U was relatively short for a chronic condition such as glaucoma; longer-term data are needed, before firm treatment recommendations can be made.

Glaucoma: topical medication

OHTS (Ocular Hypertension Treatment Study): A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma.

AUTHORS: Kass M, Heuer D, Higginbotham E *et al.*

REFERENCE: *Arch Ophthalmol* (2002) **120**, 701–13.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Decreased risk of progression to primary open-angle glaucoma (POAG) is observed with topical pressure-lowering treatment (vs no treatment) in individuals with OHT.

Impact

After clinical assessment of coexistent risk factors to identify appropriate patients, topical OHT treatment can be used to successfully decrease the likelihood of development of POAG.

Aims

Patients with OHT are at risk of developing POAG. African American populations have an incidence five times that of Caucasians. This study was designed to compare the risk of progression to POAG with and without topical OHT treatment.

Methods

Patients: 1,636 patients at 22 centres across the USA.

Inclusion criteria:

- Age 40–80y;
- IOP between 24 and 32mmHg in the first eye, and between 21 and 32mmHg in the second eye;
- Open angles;
- Normal optic discs and VFs.

Groups:

- Topical medication: Investigators free to choose any commercially available agent to lower IOP to ≤ 24 mmHg, with a minimum of 20% reduction from baseline ($n = 817$);
- No medication ($n = 819$).

Primary endpoint: Development of POAG in one or both eyes (defined as reproducible VF abnormality or reproducible optic disc deterioration attributed to POAG).

Secondary endpoints: Adverse events and SEs related to the topical medication.

Follow-up: Every 6mo for the duration of the study (median F/U 78mo).

Results

- At 60mo:

Table 27.4 Summary of results

| Primary endpoint | Treatment | No treatment | <i>p</i> |
|--|-----------|--------------|------------|
| Progression to POAG | 4.4% | 10.9% | <0.0001 |
| VF change | 1.8% | 3.5% | 0.002 |
| Optic disc change | 2.2% | 6.2% | <0.001 |
| Both field and disc changes | 0.4% | 1.1% | Not stated |
| Secondary endpoints | | | |
| Serious adverse events related to medication | None | None | — |
| SEs: ocular | 57% | 47% | <0.001 |
| SEs: skin/hair/nails | 23% | 18% | <0.001 |
| SEs: iris colour (patients on prostaglandin analogues) | 17% | 7.6% | <0.001 |

Discussion

Reducing IOP in patients with OHT reduced the risk of progression to POAG. Topical treatment was generally safe, although patients should be made aware of the potential SEs. Analysis of the African American patient subgroup showed treatment to be less protective, with a higher incidence of progression to glaucoma. A sister publication (*Arch Ophthalmol* (2002) 120, 714–20) identified baseline factors that predict POAG onset in individual subjects. (See Table 27.4.)

Problems

- The population consisted of healthy volunteers with a mean age of <60y. This may not represent patients with this condition in the general population, either in terms of outcome or medication SEs.
- The F/U of the African American subgroup was 6mo less than that for the remainder of the patients, which may have affected the results.

Glaucoma: early treatment

EMGT (Early Manifest Glaucoma Trial): Factors for glaucoma progression and the effect of treatment.

AUTHORS: Leske M, Heijl A, Hussein M *et al.*

REFERENCE: *Arch Ophthalmol* (2003) **121**, 48–56.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

IOP-lowering treatment reduces the rate of progression in some patients with early open-angle glaucoma.

Impact

This is the first large RCT to demonstrate a benefit of treatment (vs no treatment) in Caucasian patients with early glaucoma. It identifies a number of baseline characteristics that can be related to the likelihood of disease progression.

Aims

Although various factors affecting the progression of glaucoma have been studied, opinions on their relative importance and the indications for therapy vary. This prospective RCT was designed to assess the effect of IOP reduction on disease progression in early glaucoma. It also aimed to identify the other baseline factors associated with a risk of disease progression.

Methods

Patients: 255 patients at two centres in Sweden.

Inclusion criteria:

- Age 50–80y;
- Newly diagnosed, untreated open-angle glaucoma (based on the presence of repeatable glaucomatous VF defects in at least one eye, not attributable to any other cause).

Exclusion criteria:

- Advanced VF defects;
- VA <0.5 (logMAR);
- Mean IOP >30mmHg or any IOP >35mmHg in at least one eye;
- Lens or media opacities.

Groups:

- IOP-lowering treatment with argon laser trabeculoplasty, followed by topical betaxolol ($n = 129$);
- No treatment ($n = 126$).

Primary endpoint: Progression of glaucoma (defined by significant change from baseline in at least 3 points on three consecutive VF tests or change in photographic optic disc appearance). Progression of glaucoma was compared for the treatment vs no treatment group, and then assessed to determine the effect of different baseline characteristics.

Follow-up: Four pre-randomization visits, then F/U every 3mo (median 6y).

Results

Table 27.5 Summary of result

| | Progression | p |
|-----------------------------------|-------------|-------|
| Treatment group | 45% | 0.003 |
| Control group | 62% | |
| Age ≥ 68 | 57% | 0.05 |
| Age < 68 | 49% | |
| IOP ≥ 21 mmHg | 63% | 0.003 |
| IOP < 21 mmHg | 45% | |
| Mean deviation on VF ≤ -4 dB | 59% | 0.03 |
| Mean deviation on VF > -4 dB | 47% | |

- Other baseline characteristics significantly ($p < 0.001$) affecting progression were: presence of pseudoexfoliation and both eyes eligible for study (i.e. bilateral disease; progression in 72% vs 47% of those with only one eye eligible);
- Factors having no significant effect were: sex, central corneal thickness, presence of disc haemorrhage, refractive error, or personal/family medical history. (See Table 27.5.)

Discussion

Reducing IOP by 25% from baseline reduced the risk of progression by 50%. The presence of certain risk factors made progression more likely. Some patients did not progress despite receiving no treatment, and some patients progressed despite receiving pressure-lowering treatment.

Problems

- This study excluded patients with advanced glaucoma or very high IOP, so results may not be applicable to these groups.
- Only Caucasian patients were included, which may limit application of the results to other ethnic groups.
- Treatment options were limited.

Age-related macular degeneration: vascular endothelial growth factor antagonists

MPS (Macular Photocoagulation Study): Argon laser photocoagulation for neovascular maculopathy: five-year results from randomized clinical trials.

AUTHORS: The Macular Photocoagulation Study Group.

REFERENCE: *Arch Ophthalmol* (1991) **109**, 1109–14.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Intravitreal injection of ranibizumab stabilizes or improves vision in patients with minimally classic or occult choroidal neovascularization due to AMD, with few serious SEs.

Impact

Given the high incidence of AMD, ranibizumab has the potential to have a significant impact on visual outcomes and is increasingly being used in this group of patients.

Aims

In the developed world, AMD is a leading cause of blindness in patients aged >50y. Patients with neovascular AMD and minimally classic or occult lesions have poor visual prognosis, previously available treatments having shown limited success in stabilizing vision. This phase 3 trial aimed to assess the efficacy of ranibizumab (a recombinant humanized monoclonal antibody that neutralizes active VEGF in stabilizing vision).

Methods

Patients: 716 patients at 96 centres in the USA.

Inclusion criteria:

- Age ≥ 50 y;
- Best corrected VA equivalent to between 20/40 and 20/320;
- 1° or recurrent minimally classic or occult choroidal neovascularization associated with AMD, involving the fovea and ≤ 12 optic disc areas;
- Recent disease progression (determined by fresh haemorrhage, change in vision, or observed increase in lesion size).

NB. 'Classic' and 'occult' are descriptions of the appearance on fluorescein angiography.

Exclusion criteria: Previous subfoveal laser treatment, or verteporfin photodynamic therapy, or experimental treatments for wet AMD.

Groups: All patients received intravitreal injections every 1mo for 2y in one eye. Photodynamic therapy with Visudyne® was allowed, if the lesion became predominantly classic.

- Ranibizumab 0.3mg ($n = 238$);
- Ranibizumab 0.5mg ($n = 240$);
- Sham injection ($n = 238$).

Primary endpoint: Loss of <15 letters on Early Treatment of Diabetic Retinopathy Study (ETDRS) chart.

Secondary endpoints: Other adverse events (including endophthalmitis, uveitis, retinal detachment or tear, vitreous haemorrhage, and lens damage), change in VA from baseline.

Follow-up: Every 1mo for 2y.

Results

Table 27.6 Summary of result

| Primary endpoint | Ranibizumab 0.3mg ($n = 238$) | Ranibizumab 0.5mg ($n = 240$) | Sham ($n = 238$) | p |
|---------------------------|---------------------------------|---------------------------------|--------------------|------------|
| Loss of <15 letters | 94.5% | 94.6% | 62.2% | <0.001 |
| Gain of ≥ 15 letters | 24.8% | 33.8% | 5.0% | <0.001 |
| Mean change in VA | +6.5 letters | +7.2 letters | -10.4 letters | <0.001 |
| Adverse events (total) | 1.2% | 3.8% | 5.0% | Not stated |

Discussion

Clear benefits in stabilizing or improving vision were observed in patients treated with ranibizumab, as compared with control. The rate of serious adverse events was low (comparable to earlier studies), with an average rate of 1% (or 0.05% per injection) of endophthalmitis. The lower dose of ranibizumab provided as much benefit as the higher dose, with a lower rate of SEs. (See Table 27.6.)

Problems

- The numbers in the trial may have been insufficient to detect less common adverse effects of the treatment.
- The study did not look at the effect of stopping treatment on VA.

Age-related macular degeneration: ranibizumab and bevacizumab for treatment of neovascularization

CATT (Comparison Of AMD Treatments Trials): Effects of ranibizumab and bevacizumab when administered either monthly or as needed for 2 years.

AUTHORS: Comparison Of Age-Related Macular Degeneration Treatment Trials (CATT) Research Group Writing Committee.

REFERENCE: *Ophthalmology* (2012) 119, 1388–98.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Both ranibizumab and bevacizumab are safe and effective in the treatment of neovascular age-related macular degeneration (nAMD).

Impact

Treatment of nAMD with either agent is reasonable, based on efficacy and safety. The results allow for local decisions regarding drug choice and treatment regimens.

Aims

Previous trials have demonstrated benefits of treatment with either ranibizumab or bevacizumab in nAMD. This study looks at the 2y results of a direct comparison of the efficacy and safety of the two treatments.

Methods

Patients: 1,107 patients at multiple centres across the USA.

Inclusion criteria:

- Age ≥ 50 y;
- Previously untreated active subfoveal choroidal neovascularization due to AMD (confirmed on optical coherence tomography (OCT) and fluorescein angiography);
- Best corrected VA equivalent to between 20/25 and 20/320 Snellen equivalent.

Exclusion criteria:

- Previous treatment for nAMD in the study eye;
- Central fibrosis or atrophy.

Groups:

- Ranibizumab 0.5mg monthly;
- Ranibizumab 0.5mg as needed;
- Bevacizumab 1.25mg monthly;
- Bevacizumab 1.25mg as needed;
- Ranibizumab 0.5mg monthly y 1, as needed y 2;
- Bevacizumab 1.25mg monthly y 1, as needed y 2.

Primary endpoint: Mean change in VA.

Secondary endpoints: Proportion of patients with a change in VA of 15 letters or more, number of injections, change in central retinal thickness (CRT) on OCT, change in lesion size on fluorescein angiography, and incidence of systemic and ocular adverse events.

Follow-up: 24mo.

Results

Table 27.7 Summary of result

| Endpoint | R monthly | R PRN | B monthly | B PRN | p | |
|--------------------------------------|------------|------------|------------|------------|-------|---------|
| n | 134 | 264 | 129 | 251 | Drug | Regimen |
| Mean change in VA (SD) (letters) | 8.8 (15.9) | 7.8 (15.5) | 6.7 (14.6) | 5.0 (17.9) | 0.21 | 0.046 |
| Mean change in CRT (SD) (micrometre) | -190 (172) | -180 (196) | -166 (190) | -153 (189) | 0.38 | 0.08 |
| Mean no. of treatments (SD) | 22.4 (3.9) | 23.4 (2.8) | 12.6 (6.6) | 14.1 (7.0) | | 0.01 |
| One or more SAEs | 190 (31.7) | | 234 (39.9) | | 0.004 | |

B, bevacizumab 1.25mg; PRN, as needed; R, ranibizumab 0.5mg; SAE=, serious adverse events.

- In the groups switching from monthly treatment with either drug in y 1 to 'as needed' treatment in y 2, there was a mean 2.2 letter decrease, with visual results close to the 'as needed' groups. (See Table 27.7.)

Discussion

Both drugs were effective and safe in the treatment of nAMD. Significant differences were seen in visual outcomes between the dosing regimens at 2y, with monthly treatment superior to 'as needed' treatment, but these differences were clinically small. The rates of thromboembolic adverse events at 2y were similar between groups. The greater number of total serious adverse events in the bevacizumab group is unexplained.

Problems

- The preparation of single-dose units of bevacizumab was organized for the trial. These units are not available commercially at present, and results relating to infection rates should be interpreted with this in mind.

Diabetic retinopathy: laser photocoagulation

DRS (Diabetic Retinopathy Study): Photocoagulation treatment of proliferative diabetic retinopathy.

AUTHORS: The Diabetic Retinopathy Study Research Group.

REFERENCE: *Am J Ophthalmol* (1976) **81**, 383–96 and *Ophthalmology* (1978) **85**, 82–106.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Scatter argon laser photocoagulation reduces the rate of development of severe visual loss in patients with proliferative diabetic retinopathy. SEs of treatment, including loss of VA and constriction of peripheral VFs, are considered acceptable in eyes with moderate to severe retinopathy.

Impact

This was the first RCT to show the benefits of scatter laser photocoagulation in patients with proliferative diabetic retinopathy. The technique is now established worldwide as the prime treatment for this common and increasingly prevalent condition.

Aims

Patients with DM are at risk of developing proliferative retinopathy and subsequent visual impairment. Although photocoagulation had become a routine treatment, evidence for its efficacy and safety was limited. This study aimed to determine whether scatter photocoagulation was of benefit in preserving vision in these patients and whether there were differences in efficacy and safety of argon vs xenon photocoagulation.

Methods

Patients: 1,758 patients at 15 centres in the USA.

Inclusion criteria:

- Age <70y;
- Proliferative diabetic retinopathy in at least one eye or severe non-proliferative diabetic retinopathy in both eyes;
- VA of 20/100 or better in each eye.

Exclusion criteria: Previous photocoagulation.

Groups: One eye of each patient was randomly assigned to receive photocoagulation with argon ($n = 867$) or xenon ($n = 875$) laser; the second eye acted as an untreated control.

Primary endpoint: VA worse than 5/200.

Secondary endpoints:

- Loss of VA due to treatment;
- Loss of VF;
- Development or progression of proliferative retinopathy.

Follow-up: Every 4mo for up to 3y.

Results

Table 27.8 Summary of result

| Outcome | Laser groups | No laser group | Statistical significance* |
|-------------------------------|--------------|----------------|---------------------------|
| Primary endpoint | | | |
| VA worse than 5/200 at 2y | 6.4% | 15.9% | Z = 4.1 |
| VA worse than 5/200 at 3y | 10.5% | 26.4% | Z = 3.5 |
| Secondary endpoints | | | |
| ≥5 line decrease in VA at 6wk | 4.2% | 2.2% | Not stated |
| ≥5 line decrease in VA at 4mo | 6.8% | 6.1% | Not stated |
| ≥5 line decrease in VA at 1y | 10.0% | 15.9% | Not stated |
| ≥5 line decrease in VA at 2y | 13.7% | 27.1% | Not stated |

* Z value = difference between proportions of events observed in untreated and treated eyes, divided by the SE of the difference. A positive Z value indicates a lower event rate in the treated group than in the untreated group.

- Reduction in severe visual loss was greater in the xenon group, compared with the argon group. (See Table 27.8.)
- Xenon treatment carried a greater risk of loss of ≥5 lines of VA than treatment with argon or no treatment.
- There was substantial loss of peripheral VF in the xenon group (only 48% retained ≥500° of field, compared to 90% in the other groups).
- There was a statistically significant reduction in the progression of all stages of retinopathy seen in the treatment groups (vs no treatment).

Discussion

The DRS study commenced in 1971. It showed photocoagulation to be effective in reducing severe visual loss (by >50%) in eyes with proliferative diabetic retinopathy and the development of high-risk characteristics across all stages of diabetic retinopathy. Xenon treatment led to a marked impairment of peripheral VF, more so than argon treatment. Persistent decreases in VA were twice as common in xenon-treated eyes than in those treated with argon.

Problems

- Eyes in which severe macular oedema or ischaemia reduced VA to worse than 20/100 were excluded from this study.
- As this study was a comparison of immediate treatment vs no treatment, the possibility of deferred treatment in eyes with severe non-proliferative or mild proliferative retinopathy was not considered.

Diabetic retinopathy: photocoagulation for macular oedema

ETDRS (Early Treatment of Diabetic Retinopathy Study): Report number 1. Photocoagulation for diabetic macular edema.

AUTHORS: Early Treatment Diabetic Retinopathy Study Group.

REFERENCE: *Arch Ophthalmol* (1985) 103, 1796–806.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Eyes with clinically significant macular oedema associated with mild to moderate non-proliferative diabetic retinopathy benefit from treatment with focal argon laser treatment.

Impact

This trial defined a subtype of macular oedema in patients with mild to moderate non-proliferative diabetic retinopathy that benefits from focal argon laser treatment and is now normally treated. Macular oedema outside this classification carries a low risk of visual loss and need not be treated. Another arm of this study concluded aspirin therapy to have no ocular contraindications in patients with diabetes, hence not requiring for it to be withheld when required for other indications.

Aims

Diabetic retinopathy causes visual loss through macular oedema, ischaemia, or proliferative disease. The ETDRS was designed to evaluate photocoagulation and aspirin treatment in the management of non-proliferative and early proliferative diabetic retinopathy. This first report looked at the question of whether argon laser photocoagulation was effective in the treatment of diabetic macular oedema. The study also considered when pan-retinal photocoagulation (PRP) treatment was most effective and whether aspirin treatment could alter the course of disease.

Methods

Patients: 1,876 patients (2,998 eyes) at 23 centres across the USA.

Inclusion criteria:

- Age 18–70y;
- Presence of mild to moderate diabetic retinopathy with clinically significant macular oedema (CSMO). Defined as ≥ 1 of:
 - Retinal thickening at or within 500 micrometres of the centre of the macula;
 - Hard exudates at or within 500 micrometres of the centre of the macula associated with retinal thickening;
 - Retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula;
- VA of 20/200 or better (with macular oedema).

Exclusion criteria: Other significant ocular disease.

Groups:

- Immediate focal argon laser photocoagulation (repeated, if CSMO persisted or developed during F/U) ($n = 1,508$ eyes);
- No treatment ($n = 1,490$ eyes).

Primary endpoint: Loss of ≥ 15 letters of VA.

Secondary endpoints:

- VF loss;
- Change in colour vision score (Farnsworth–Munsell 100 hue test).

Follow-up: At 6mo, then every 4mo for 3y.

Results

Table 27.9 Summary of result

| % eyes with VA loss ≥ 15 letters | Laser group | No laser group | p |
|---------------------------------------|-------------|----------------|------|
| At 1y | 5% | 8% | 0.01 |
| At 2y | 7% | 16% | 0.01 |
| At 3y | 12% | 24% | 0.01 |

- Similar differences between groups for final VA < 50 letters ($= 20/100$).
- For eyes with CSMO at time of recruitment, 35% had persistent CSMO at 1y in the laser group, compared to 63% in the no laser group. (See Table 27.9.)
- No significant differences seen between groups for VFs or colour vision.

Discussion

This study showed that, for eyes with macular oedema associated with mild to moderate diabetic retinopathy, immediate laser photocoagulation reduced the proportion of eyes with significant visual loss. Visual prognosis was worse for eyes with a poorer VA at baseline. For eyes without CSMO, the rate of visual loss was low, with no benefit of laser treatment. The authors recommended that all eyes with CSMO associated with mild to moderate non-proliferative diabetic retinopathy be treated and that treatment also be considered in eyes with CSMO associated with severe non-proliferative or proliferative disease. Further reports from the same study group showed that the benefit of PRP treatment outweighed the risks when carried out early in eyes exhibiting high-risk features. Eyes with mild to moderate non-proliferative retinopathy carried low risk of progression, and deferral of treatment was recommended. Another arm of this study (which randomized patients to 650mg od aspirin vs placebo) found no effect of aspirin on the progression of diabetic retinopathy or the development of preretinal or vitreous haemorrhage. Its use at a lower dose was associated with a 17% decrease in morbidity and mortality.

Problems

- Only a few patients with severe non-proliferative or proliferative diabetic retinopathy were included in the macular oedema part of the trial, so it is difficult to be certain about the magnitude of the treatment effect in these patients.

Diabetic retinopathy: laser and vascular endothelial growth factor antagonists for macular oedema

Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema

AUTHORS: Diabetic Retinopathy Clinical Research (DRCR) Network.

REFERENCE: *Ophthalmology* (2010) 117, 1064–77.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Eyes with centre-involving diabetic macular oedema show superior VA gains and optical coherence tomography (OCT) outcomes, when treated with intravitreal ranibizumab plus either prompt or deferred laser vs treatment with laser alone. Similar improvements are seen in pseudophakic eyes with intravitreal triamcinolone.

Impact

Laser was previously the gold standard treatment for diabetic macular oedema. This study was the first to quantify the effect of ranibizumab treatment in eyes with centre-involving macular oedema and has changed practice where funding for such treatment is available.

Aims

Macular laser was the previous gold standard for treatment of diabetic macular oedema. This study compares treatment with macular laser alone and macular laser combined with intravitreal ranibizumab 0.5mg or triamcinolone 4mg in the treatment of centre-involving diabetic macular oedema.

Methods

Patients: 854 eyes of 691 participants at 52 clinical sites in the USA.

Inclusion criteria:

- Age ≥ 18 y;
- Type 1 or type 2 diabetes;
- Best corrected VA equivalent to between 20/32 and 20/320;
- Diabetic macular oedema involving the fovea;
- CRT on OCT > 250 micrometres.

Exclusion criteria:

- Treatment for diabetic macular oedema in the preceding 4mo;
- PRP in the preceding 4mo or likely to be needed in the next 6mo;
- Ocular surgery in the preceding 4mo;
- Open-angle glaucoma, IOP > 25 mmHg, or known steroid response;
- Systemic contraindication to anti-VEGF therapy.

Groups:

- Sham injection plus prompt laser ($n = 293$);
- Ranibizumab 0.5mg plus prompt laser ($n = 187$);
- Ranibizumab 0.5mg plus deferred (≥ 24 wk) laser ($n = 186$).

Primary endpoint: Change in VA at 1y.

Secondary endpoints: Change in VA at 2y, change in CRT on OCT, adverse events including raised IOP and cataract surgery

Follow-up: Every month, for 2y.

Results

Table 27.10 Summary of result

| Endpoint | Sham injection + prompt laser ($n = 293$) | Ranibizumab 0.5mg + prompt laser ($n = 187$) | Ranibizumab 0.5mg + deferred laser ($n = 188$) | Triamcinolone 4mg and prompt laser ($n = 186$) |
|--|---|--|--|--|
| Change in VA 1y (letters), mean \pm SD | +3 \pm 13 | +9 \pm 11 ($p < 0.001$) | +9 \pm 11 ($p < 0.001$) | +4 \pm 13 ($p = 0.33$) |
| Change in VA 2y (letters), mean \pm SD | +2 \pm 16 | +7 \pm 13 ($p = 0.01$) | +10 \pm 15 ($p < 0.001$) | 0 \pm 21 ($p < 0.001$), decrease |
| Change in CRT 1y | -102 \pm 151 | -131 \pm 129 ($p < 0.001$) | -137 \pm 136 ($p < 0.001$) | -127 \pm 140 ($p < 0.001$) |
| Elevated IOP (2y) | 32 (11%) | 20 (11%) | 14 (7%) | 93 (50%) |
| Cataract surgery (2y) | 23 (12%) | 16 (12%) | 17 (13%) | 68 (55%) |

Discussion

Treatment of centre-involving macular oedema with intravitreal ranibizumab plus prompt or deferred laser is more effective at 1y than sham injection plus laser. In pseudophakic eyes, treatment with intravitreal triamcinolone plus laser seems more effective than treatment with laser alone but carries a risk of raised IOP. (See Table 27.10.)

Problems

- The preparation of triamcinolone used in the study is not available in the UK. These results cannot be applied to different drug preparations.
- Further F/U is required to see whether the benefit lasts beyond 2y.

Retinal vein occlusion: intravitreal dexamethasone implant for macular oedema

Evaluation of dexamethasone intravitreal implant in eyes with vision loss due to macular oedema associated with branch or central retinal vein occlusion.

AUTHORS: Haller J, Bandello F, Belfort R *et al.* (GENEVA Study Group).

REFERENCE: *Ophthalmology* (2010) 117, 1134–46.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Intravitreal dexamethasone (DEX) implants are effective in treating macular oedema, following both branch (BRVO) and central retinal vein occlusion (CRVO).

Impact

Treatment of macular oedema in retinal vein occlusion has previously been limited to laser in BRVO only. This study showed that intravitreal dexamethasone implants are effective in treatment of macular oedema following both BRVO and CRVO.

Aims

Previous studies have demonstrated a benefit for laser in the treatment of macular oedema following BRVO, but not CRVO. This study investigated whether the use of an intravitreal DEX implant is effective in the treatment of macular oedema in both conditions, compared to sham.

Methods

Patients: 1,267 participants at 167 clinical sites in 24 countries.

Inclusion criteria:

- Age ≥ 18 y;
- Best corrected VA between 20/50 and 20/320 (equivalent);
- Macular oedema following either BRVO or CRVO for between 6wk and 9mo with CRVO or 12mo with BRVO;
- CRT on OCT >300 micrometres.

Exclusion criteria:

- Clinically significant epiretinal membrane;
- Ocular neovascularization;
- Active infection;
- Glaucoma or OHT requiring >1 agent to control IOP.

Groups: Allocated in a 1:1:1 ratio:

- Sham procedure ($n = 426$);
- 0.35mg DEX implant ($n = 414$);
- 0.7mg DEX implant ($n = 427$).

Primary endpoint: Time to reach a 15-letter gain.

Secondary endpoints: Proportion of eyes reaching a 10- to 15-letter gain, proportion with ≥ 15 letter worsening, mean change from baseline VA. CRT on OCT, IOP rise, cataract.

Follow-up: 180d.

Results

Table 27.11 Summary of result

| Endpoint | DEX implant 0.7mg | DEX implant 0.35mg | Sham | p vs sham 0.35mg/0.7mg |
|---|----------------------|-----------------------|----------------|---------------------------|
| Change in CRT d 90 (micrometre \pm SD) | -208 ± 201 | -177 ± 197 | -85 ± 173 | $<0.001/$ <0.001 |
| Change in CRT d 180 (micrometre \pm SD) | -119 ± 203 | -123 ± 212 | -119 ± 188 | ns/ns |
| Elevated IOP | 17 (4%) | 16 (3.9%) | 3 (0.7%) | 0.001/0.002 |
| Cataract | 31 (7.3%) | 17 (4.1%) | 19 (4.5%) | ns/ns |

ns, non-significant.

Discussion

Intravitreal DEX implants are effective in reducing macular oedema, following either BRVO or CRVO. This effect reduces over time, with no difference in OCT thickness seen between groups at 180d. The implants seem safe but do carry a risk of elevated IOP. This peaks at 60d, returning to normal by 180d. (See Table 27.11.)

Problems

- There was no direct comparison between the DEX implant and macular laser for macular oedema in BRVO.
- Patients did not undergo fluorescein angiography at entry to the trial to exclude those with significant ischaemia.

Myopia: surgical correction

Evidence for superior efficacy and safety of LASIK over photorefractive keratectomy for correction of myopia.

AUTHORS: Shortt A, Bunce C, Allan B.

REFERENCE: *Ophthalmology* (2006) **113**, 1897–908.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Laser-assisted *in situ* keratomileusis (LASIK) is safer and more effective than photorefractive keratectomy (PRK) for the correction of myopia.

Impact

This meta-analysis of trials conducted in the 1990s revealed LASIK to be a safer and more effective method of refractive surgery to correct myopia than PRK. However, it did not consider other procedures for myopia (such as Epi-LASIK or LASEK), which may be preferred in certain clinical scenarios.

Aims

Two of the commonest surgical treatments for the correction of myopia are LASIK and PRK. LASIK involves the creation of a thin corneal flap that is folded back, while laser is used to reshape the corneal stroma, and is then replaced at the end of the procedure. With PRK, the epithelium is removed surgically, before an excimer laser is used to reshape the anterior stroma. The epithelium regrows over a few days. This meta-analysis of prospective RCTs compared the safety and efficacy of these two types of refractive surgery in the correction of myopia.

Methods

Patients: Seven trials with a total of 683 eyes undergoing PRK, and 403 undergoing LASIK.

Inclusion criteria:

- Prospective RCT comparing LASIK and PRK;
- Correction of any myopia or ≤ 3 dioptres of astigmatism;
- Age 18–60y;
- No ocular co-pathology or previous surgery;
- No systemic condition that could be associated with impaired wound healing.

Outcome measures:

- Efficacy:
 - Uncorrected VA (UCVA) $\geq 20/20$;
 - Post-operative spherical equivalent within ± 0.50 dioptres from target.

Safety:

- Loss of ≥ 2 lines best spectacle-corrected VA (BSCVA);
- Final BSCVA $<20/40$;
- Final BSCVA $<20/25$ when initial BSCVA $\geq 20/20$.

Results**Table 27.12** Summary of result

| Outcome measure | No. of trials | Procedure | OR | p |
|--|---------------|--|------|------------|
| UCVA better than 20/20 at 6mo | 7 | LASIK | 1.72 | 0.009 |
| UCVA better than 20/20 at 12mo | 5 | LASIK | 1.78 | 0.01 |
| Post-op SE \pm 0.5D at 6mo | 4 | No significant difference | 0.83 | Not stated |
| Post-op SE \pm 0.5D at 12mo | 5 | Trend towards LASIK, but no significant difference | 1.38 | 0.1 |
| Loss ≥ 2 lines BSCVA | 5 | PRK | 2.69 | 0.05 |
| Final VA $<20/40$ | 4 | Trend towards PRK, but no significant difference | 2.92 | 0.4 |
| Final VA $<20/25$ when initial VA $>20/20$ | 4 | No significant difference | 0.93 | Not stated |

SE, spherical equivalent.

- Subgroup analysis of patients with correction of low myopia (< -6.0 dioptres) showed similar results. (See Table 27.12.)

Discussion

Analysis of the trials considered in this paper demonstrated the efficacy and safety of LASIK to be superior to that of PRK. This was supported by parallel analysis of a number of prospective case series, as described within the paper.

Problems

- Data collated and examined for this study related to trials conducted 5 or more years ago, which may not have included new techniques and modifications to existing techniques.
- A 1y F/U period may be insufficient to allow complete recovery from the procedure.
- Outcome measures between the trials were not standardized, making comparison more difficult.

Ocular herpes simplex: antiviral treatment

HEDS-APT (Herpetic Eye Disease Study–Acidoclovir Prevention Trial): Acyclovir for the prevention of recurrent herpes simplex virus eye disease.

AUTHORS: The Herpetetic Eye Disease Study Group.

REFERENCE: *N Engl J Med* (1998) **339**, 300–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Use of oral aciclovir over a 1y period reduces the risk of recurrence of ocular herpes simplex eye disease.

Impact

Ocular herpes simplex is a recurrent condition. Stromal keratitis and uveitis can cause a decrease in vision, due to scarring. Use of oral aciclovir over a 12mo period reduces the risk of recurrent disease.

Aims

Ocular herpes simplex is a recurrent condition that can affect different parts of the eye. Complications, including stromal keratitis and uveitis, can cause visual loss, due to scarring. Although aciclovir had been previously used in this condition, there was no consensus as to its role in treatment and prevention. This study aimed to evaluate the effect of treatment with oral aciclovir in reducing the recurrence rate of ocular HSV disease.

Methods

Patients: 703 patients at 74 clinical centres in the USA.

Inclusion criteria:

- Age ≥ 12 y;
- Episode of ocular HSV in one or both eyes within the last 1y, but not within the last 30d;
- Immunocompetent, on no antiviral or topical treatment;
- No previous corneal surgery;
- No contraindication to treatment with aciclovir.

Groups:

- Oral aciclovir (400mg bd for 1y) ($n = 357$);
- Placebo ($n = 346$);

Both groups then stopped treatment but remained under observation for a further 6mo.

Primary endpoint: One episode of recurrence of ocular HSV disease.

Secondary endpoints:

- Multiple episodes of recurrence of ocular HSV disease;
- SEs or serious adverse events related to medication.

Follow-up: Examinations at 1, 3, 6, 9, and 12mo during treatment. Post-treatment observation at 13, 15, and 18mo. Recurrence = ocular surface infections, stromal keratitis, or iritis.

Results

Table 27.13 Summary of result

| Primary endpoint | Aciclovir | Placebo | <i>p</i> |
|--|-----------|---------|------------|
| Recurrence of ocular HSV disease during treatment period | 19% | 32% | <0.001 |
| Recurrence of ocular HSV disease after treatment period | 13% | 14% | ns |
| Secondary endpoints | | | |
| >1 episode of recurrence | 4% | 9% | Not stated |
| Medication discontinued due to SEs | 4% | 5% | Not stated |
| Serious adverse events | 0 | 0 | — |

Discussion

The HEDS-II study comprises two RCTs evaluating the role of oral aciclovir in the management of HSV eye disease. This study showed a significant reduction in the number of recurrences of ocular HSV disease in patients treated with long-term oral aciclovir. This effect did not persist after stopping medication, but no rebound effect was seen. There was no difference in the rate of SEs between the groups, and no adverse events in either group. Patients with stromal keratitis and uveitis are at greatest risk of long-term visual loss, particularly if the disease is recurrent. The sister trial (HEDS-EKT ‘epithelial keratitis trial’) evaluated the benefits of oral aciclovir treatment for acute HSV keratitis, finding no benefit from the addition of oral aciclovir to topical trifluridine in preventing stromal keratitis or iridocyclitis. A study evaluating the effect of other factors (psychological, environmental, and biological) on recurrences of HSV eye disease is currently under way (HEDS-RFS ‘recurrence factor study’). (See Table 27.13.)

Problems

- This study considered immunocompetent patients only; it is impossible to say with certainty whether the result would also apply to immunocompromised patients.
- These results may not be relevant to patients who have undergone corneal grafting, as they were excluded from this study.

Otorhinolaryngology

- Introduction 766
- Otitis externa: topical drops 768
- Acute otitis media: antibiotics 770
- Otitis media with effusion: grommets 772
- Otitis media with effusion: adjuvant adenoidectomy 774
- Benign paroxysmal positional vertigo: Epley's manoeuvre 776
- Chronic dizziness: booklet-based vestibular rehabilitation 778
- Acute rhinosinusitis: antibiotics 780
- Recurrent upper respiratory tract infections in children: adenoidectomy 782
- Chronic rhinosinusitis with moderate to severe nasal polyposis: oral steroids followed by intranasal steroids 784
- Acute sore throats in children: penicillin 786
- Childhood obstructive sleep apnoea: adenotonsillectomy 788
- Severe obstructive sleep apnoea: surgery vs positive airway pressure 790
- Laryngopharyngeal reflux: proton pump inhibitors 792

Introduction

Conditions of the ear, nose, and throat (ENT) are among the commonest diagnoses in 1° care in both children and adults and are a frequent indication for referral to 2° care. They have a major impact on health and health-care resources, and it is therefore important that the management of ENT conditions is based upon the best available evidence. Such evidence should come from methodologically sound research in patients representative of those seen in everyday practice—both in 1° and 2°. Over the past decades, GPs and ENT surgeons have increasingly embraced the principles of EBM, actively contributed to RCTs in this field, and supported Cochrane Groups like those on acute respiratory infections and ENT disorders. With this, management of ENT conditions is shifting from experience-based to evidence-based.

As in many other conditions, patients' expectations towards the benefits of common treatments in ENT tend to be high; it is up to the GP and ENT surgeon to manage these expectations and weigh the benefits against the potential risks of these interventions together with the patient. The RCTs and individual patient data (IPD) meta-analyses presented in this chapter have been instrumental in the development of clinical guidelines that allow GPs and ENT surgeons to make evidence-based shared decisions for the management of some of the commonest ENT conditions.

Otitis externa: topical drops

Clinical efficacy of three common treatments in acute otitis externa in primary care: randomised controlled trial.

AUTHORS: van Balen F, Smit W, Zuithoff N *et al.*

REFERENCE: *BMJ* (2003) 327, 1201–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Ear drops containing corticosteroids are more effective than those containing acetic acid alone for the treatment of acute otitis externa in 1° care. Corticosteroid and acetic acid ear drops are just as effective as those containing corticosteroid and antibiotics.

Impact

For mild cases of acute otitis externa, corticosteroid and acetic acid ear drops appear justified. For more severe cases, or if treatment with corticosteroid and acetic acid ear drops fails, corticosteroid and antibiotic ear drops should be considered.

Aims

Acute otitis externa is a common condition, often predisposed to by persistently moist environments. Control of itching symptoms is improved by over-the-counter medications containing acetic acid. In 1° and 2° care, antibiotic drops (with and without corticosteroids) are commonly prescribed. With no consensus as to which treatment was optimal, this study aimed to compare the clinical efficacy of ear drops containing acetic acid alone, corticosteroid and acetic acid, and corticosteroid and antibiotics in the treatment of acute otitis externa in 1° care.

Methods

Patients: 213 patients from 47 GPs in The Netherlands.

Inclusion criteria:

- Acute otitis externa (redness or swelling of the ear canal or debris within the canal, with pain, itchiness, discharge, or hearing loss for <3wk);
- Age >17y.

Exclusion criteria:

- Chronic otitis externa;
- Furuncle in the ear canal;
- Acute otitis media (AOM);
- Perforated eardrum;
- Treatment for acute otitis externa in the past month.

Groups:

- Acetic acid 7.2mg/g, three drops tds ($n = 71$);
- Triamcinolone 0.1% and acetic acid, three drops tds ($n = 63$);
- Dexamethasone 0.66 mg, 5mg neomycin, and 10,000IU polymyxin/mL, three drops tds ($n = 79$).

NB. Any patient whose eardrum could not be visualized at baseline had a dry wick placed in the ear canal for 24h, with the drops applied to it. After 24h, the wick was removed, and the ear inspected. This was continued, until the eardrum was visible and the drops could penetrate the ear canal.

Randomization, allocation concealment, and blinding:

- Computer-generated randomization list drawn by statistician;
- Hospital pharmacy supplied practices with identical bottles, each containing 10mL drops, numbered according to the randomization list;
- To ensure blinding, a practice assistant not involved in evaluating the patients applied the first dose of drops during the baseline visit.

Follow-up and measurements: Baseline (initial visit), F/U visits at d 7 and 14. Patients who had not recovered at d 14 continued treatment until d 21. Patients completed a standardized daily symptom diary. Telephone questionnaire completed at d 42.

Primary outcome: Duration of symptoms in days, as measured by the patient diary.

Secondary outcomes: Cure rates at d 6–8, 13–15, and 20–22, and symptom recurrence between d 21 and 42.

Results

Table 28.1 Summary of result

| Cure rates | d 7 | d 14 | d 21 |
|--------------------------------|-------|--------|--------|
| Acetic acid | 19/65 | 37/65 | 40/65 |
| Corticosteroid and acetic acid | 29/61 | 46/61* | 54/61* |
| Corticosteroid and antibiotic | 31/73 | 60/73* | 63/73* |

* Statistically significant difference when compared to acetic acid ($p = 0.001$).

- The cure rates at d 14 and 21 were significantly lower in the acetic acid only group than those in the other groups (see Table 28.1);
- The median duration of symptoms differed significantly between the groups: 8d (95% CI 7.0–9.0) in the acetic acid only group vs 7d (95% CI 5.8–8.3) in the corticosteroid and acetic acid group, and 6d (95% CI 5.1–6.9) in the corticosteroid and antibiotic group.

Discussion

This double-blind RCT of high methodological quality showed that ear drops containing corticosteroids were more effective in the treatment of adult patients with acute otitis externa than those containing acetic acid alone. Corticosteroid and acetic acid drops reduced the duration of symptoms by 1d, compared to corticosteroid and antibiotic drops. This is important, as topical antibiotic drops may cause local hypersensitivity and may contain potentially ototoxic aminoglycosides. For patients with continued symptoms and ear canal debris, aural toilet appeared useful. As this option is often not available in 1° care, referral may be required in these cases.

Acute otitis media: antibiotics

Antibiotics for acute otitis media: a meta-analysis with individual patient data.

AUTHORS: Rovers M, Glasziou P, Appelman C *et al.*

REFERENCE: *Lancet* (2006) **368**, 1429–35.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

Overall, antibiotics provide limited benefit in children with AOM. This IPD meta-analysis shows that antibiotics are most beneficial in children aged <2y with bilateral AOM, and in children with both AOM and concurrent discharge.

Impact

For most children suffering from mild symptoms of AOM, initial observation is justified. Subgroups of children in which immediate treatment with antibiotics should be considered are young children (aged <2y) with bilateral disease and those suffering from AOM and concurrent discharge.

Aims

AOM is one of the commonest infectious diseases in children. Although antibiotics are frequently used in clinical practice, evidence from RCTs and systematic reviews suggests their benefits are limited. With issues, including growing antimicrobial resistance and adverse effects of antibiotic use, it is important that subgroups of children who are likely to benefit more from antibiotics are identified. This study assessed the effectiveness of antibiotics in children with AOM through an IPD meta-analysis, thus providing the power to perform reliable subgroup analyses.

Methods

Literature search using the Cochrane Library, PubMed, EMBASE, and the proceedings of the international symposia on otitis media to identify relevant RCTs. 1° investigators of eligible trials were asked to provide raw data.

Inclusion criteria:

- Placebo-controlled RCTs of high methodological quality;
- Participants aged <12y with AOM;
- Trials including pain and fever as an outcome.

Primary outcome:

- Extended course of AOM; pain, fever (>38°C), or both at 3–7d.

Secondary outcomes:

- Pain at 3–7d;
- Fever (>38°C) at 3–7d;
- Adverse effects of antibiotics.

Effect modifiers included in the IPD meta-analysis: Age (<2 vs ≥2y), fever, bilateral AOM, concurrent otorrhoea at baseline.

Results

- Raw data available for six out of ten eligible trials;
- The risk of an extended course of AOM was lower in children treated with antibiotics, compared to those treated with placebo: risk difference (RD) 13% (95% CI 9–17%), NNT 8;
- The effect of antibiotics was modified by age and bilaterality of the disease, and by discharge (see Table 28.2).
- Children treated with antibiotics more often had a greater number of episodes of diarrhoea (4–21% vs 2–14%) and rash (1–8% vs 2–6%), compared to those treated with placebo;
- One child in the placebo group developed meningitis at d 3 of the study but did receive antibiotics after 2d because of deterioration. No cases of mastoiditis or other serious complications were reported.

Table 28.2 Summary of result

| Extended course of AOM | Antibiotics (n = 819) | Placebo (n = 824) | RD (95% CI) | Interaction, p |
|---------------------------|-----------------------|-------------------|-------------------|----------------|
| Age and bilateral AOM: | | | | 0.022 |
| <2y + bilateral AOM | 30% | 55% | –25% (–36 to –14) | |
| <2y + unilateral AOM | 35% | 40% | –5% (–17 to 7) | |
| ≥2y + bilateral AOM | 23% | 35% | –12% (–25 to 1) | |
| ≥2y + unilateral AOM | 19% | 26% | –7% (–14 to 0) | |
| Concurrent ear discharge: | | | | 0.039 |
| Yes | 24% | 60% | –36% (–53 to –19) | |
| No | 28% | 42% | –14% (–23 to –5) | |

Discussion

Compared with placebo, treatment with antibiotics resulted in fewer children with ear pain, fever, or both at d 3–7. Absolute risk differences between treatment groups were rather small (NNT = 8), as most children with AOM settle spontaneously. Antibiotics were most beneficial in young children (aged <2y) with bilateral disease (NNT = 4) and in those suffering from AOM and concurrent discharge (NNT = 3). These benefits of antibiotics should be carefully weighed against their possible harms, including adverse effects like diarrhoea and rash, and the risk of increased antimicrobial resistance.

Problems

All included trials were conducted in Western countries; therefore, these results may not be applicable to populations with higher risk of complications.

Otitis media with effusion: grommets

Grommets in otitis media with effusion: an individual patient data meta-analysis.

AUTHORS: Rovers M, Black N, Browning G *et al.*

REFERENCE: *Arch Dis Childhood* (2005) **90**, 480–5.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

For most children with otitis media with effusion (OME), watchful waiting is an appropriate management option. Young children attending day care and children aged ≥ 4 y with a hearing loss of ≥ 25 dB in both ears and persisting for ≥ 12 wk benefit most from grommets.

Impact

A period of watchful waiting for at least 3mo is recommended for all children suffering from OME before considering grommet insertion.

Aims

Grommets (also known as ventilation tubes) are frequently inserted in children with OME. Trials to date have demonstrated limited benefits of grommets in hearing and language development. While some of these trials suggested a greater benefit in certain subgroups of children, they were too underpowered to draw valid and reliable conclusions from subgroup analyses. This IPD meta-analysis aimed to provide sufficient power to perform reliable subgroup analyses and identify children with OME who might benefit, more than others, from grommets.

Methods

Literature search using PubMed, proceedings of international symposia on otitis media, and the Cochrane Library to identify relevant RCTs. 1° investigators of all eligible trials were asked to provide their raw data.

Inclusion criteria:

- RCTs with high methodological quality;
- Age of participants <12 y;
- Persistent bilateral OME confirmed by tympanometry and/or otoscopy;
- Comparison: grommets vs watchful waiting (WW).

Primary outcomes:

- Mean time spent with effusion (measured by tympanometry);
- Hearing (pure tone audiogram or age-appropriate assessment);
- Language development (Reynell test).

Effect modifiers included in the IPD meta-analysis: Baseline hearing, history of AOM or upper respiratory tract infections, day-care attendance, gender, age, socio-economic status, siblings, season, breastfeeding, and parental smoking.

Results

- Raw data available for seven out of ten eligible trials. Four trials ($n = 801$) treated both ears of children with OME with grommets or WW, while three trials ($n = 433$) treated only one ear and used the contralateral ear as comparison;
- During 1y F/U, children treated with grommets had 19.7wk with effusion vs 37wk in the WW group ($p < 0.001$);
- Language development same for both groups at 6–9 and 12–18mo.
- Mean hearing levels were (see Table 28.3):

Table 28.3 Summary of result

| F/U period | Treatment group | <i>n</i> | Mean HL (dB) | <i>p</i> |
|------------|-----------------|----------|--------------|----------|
| Baseline | Grommets | 296 | 40.1 | 0.4 |
| | WW | 278 | 39.3 | |
| 6mo | Grommets | 192 | 26.6 | 0.001 |
| | WW | 189 | 31.1 | |
| 12mo | Grommets | 198 | 27.3 | 0.8 |
| | WW | 181 | 27.6 | |
| 18mo | Grommets | 148 | 20.7 | 0.7 |
| | WW | 135 | 20.2 | |

F/U, follow-up; HL, hearing level; WW, watchful waiting.

- Statistically significant interaction effects were found at 6mo for:
 - Young children attending day care and receiving grommets (7dB better hearing than those managed by WW. In children not attending day care, this difference was 0.9dB; $p = 0.02$ for interaction);
 - Children $\geq 4y$ with hearing poorer than 25dB in both ears persisting for $\geq 12wk$ and receiving grommets (10dB better hearing than those who did not receive grommets. In children with initial hearing better than 25dB, this difference was 4dB of hearing level; $p = 0.05$ for interaction).

Discussion

Previous trials demonstrated only marginal effects of grommets on hearing and language development. The most frequently cited (Paradise *et al.* *N Engl J Med* (2001) **344**, 1179–87), not included in this meta-analysis, demonstrated no benefit, in terms of developmental outcomes at 3y, between children with persistent OME receiving grommets either immediately or delayed (9mo later if effusion persisted). This meta-analysis added to this message—most children with OME can be safely watched for some time. Moreover, this IPD showed that day-care attendance and hearing loss worse than 25dB in both ears in older children (aged $\geq 4y$) were associated with hearing differences. The findings of this IPD meta-analysis have been included in the 2008 UK's NICE guidelines on the surgical management of OME.

Otitis media with effusion: adjuvant adenoidectomy

Adjuvant adenoidectomy in persistent bilateral otitis media with effusion: hearing and revision surgery outcomes through 2 years in the TARGET randomised trial.

AUTHORS: MRC Multicentre Otitis Media Study Group

REFERENCE: *Clin Otolaryngol* (2012) **37**, 107–16.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In children aged 3–7y with persistent otitis media with effusion (pOME) and hearing loss of ≥ 20 dB in both ears, adjuvant adenoidectomy extended better hearing through the second year post-operatively (benefit: 4.2dB) and reduced eligibility for revision surgery.

Impact

Adenoidectomy adjuvant to grommet insertion appeared to be more effective than grommets alone in children with pOME and bilateral hearing loss of ≥ 20 dB. However, the absolute benefits on hearing levels were modest.

Aims

In general, grommets offer only marginal benefit in children with pOME, compared to watchful waiting alone. However, benefits may be more prominent, if adjuvant adenoidectomy is performed. This trial reported the adjuvant effects of adenoidectomy to grommets, in terms of hearing thresholds and revision surgery, in children aged ≥ 3.5 y with pOME.

Methods

Patients: 376 children recruited from 11 ENT departments in the UK.

Inclusion criteria:

- Bilateral pOME (confirmed by tympanometry) for ≥ 3 mo, with an average hearing level in the better ear of 20dB or worse;
- Age between 39mo and 81mo.

Groups:

- Grommets only ($n = 126$);
- Grommets and adenoidectomy ($n = 128$);
- Watchful waiting (WW) ($n = 122$).

Randomization and allocation concealment: In this open-label trial, randomization was performed centrally by telephone. For each centre, the first five children were randomized, according to a computer-generated random number sequence. Thereafter, treatment allocations were balanced through a minimization procedure. The basis of minimization was not divulged to the participating centres.

Follow-up measurements: Baseline (initial visit); F/U visits at 3, 6, 12, 18, and 24mo. At each visit, otoscopy was performed, and air conduction hearing thresholds at 0.5, 1.0, 2.0, and 4.0kHz in each ear were summarized as the 4-frequency average binaural hearing thresholds.

Primary outcomes:

- Hearing level;
- Audiometrical eligibility for revision surgery.

Results

- Averaged over 3–6mo post-operatively, adenoidectomy did not add to the benefit to hearing of grommets (8.8dB, 95% CI 7.1–10.5);
- Averaged over the second year post-operatively, adjuvant adenoidectomy provided 4.2dB of benefit (95% CI 2.6–5.7), while grommets alone gave no benefit;
- Adjuvant adenoidectomy reduced audiometric eligibility for revision surgery and actual surgery rates, compared to grommets alone: 13% vs 34% (ARR of 21%). (See Table 28.4.)

Table 28.4 Summary of result

| F/U period | Treatment group | SD | Mean HL (dB) (95% CI) | TES |
|---------------------|-----------------|-----|-----------------------|-------|
| 3–6mo average | Grommets | 6.2 | 15.9 (14.8–17.0) | 1.28 |
| | Grommets + A | 6.1 | 14.6 (13.6–15.7) | 1.50 |
| | WW | 7.7 | 24.7 (23.3–26.1) | |
| 12–18–24mo average | Grommets | 6.5 | 20.1 (19.0–21.2) | –0.14 |
| | Grommets + A | 5.9 | 15.9 (14.9–17.0) | 0.55 |
| | WW | 6.2 | 19.4 (18.3–20.5) | |
| 2y combined average | Grommets | 5.2 | 18.5 (17.6–19.5) | 0.50 |
| | Grommets + A | 5.3 | 15.5 (14.5–16.4) | 1.11 |
| | WW | 5.6 | 21.4 (20.4–22.4) | |

A, adenoidectomy; F/U, follow-up; HL, hearing level; SD, standard deviation; TES, standardized treatment effect size (ratio of mean difference between the two treatment groups in question to the pooled SD); WW, watchful waiting.

Discussion

This trial showed that the average short-term benefit to hearing from grommets disappears by 12mo in children aged ≥ 3.5 y with pOME, with an initial average hearing level in the better ear of ≥ 20 dB. However, adjuvant adenoidectomy extends the benefit to hearing through the second year (benefit: 4.2dB). Moreover, adjuvant adenoidectomy reduced audiometric eligibility for revision surgery, compared to grommets alone.

Problems

- These results are applicable only to children with pOME with stringent inclusion criteria (seven out of ten children failed audiometry and/or tympanometry criteria), and the absolute benefits of surgery are modest.

Benign paroxysmal positional vertigo: Epley's manoeuvre

Short-term efficacy of Epley's manoeuvre: a double-blind randomised trial.

AUTHORS: von Brevern M, Seelig T, Radtke A *et al.*

REFERENCE: *J Neurol Neurosurg Psychiatry* (2006) 77, 980–2.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Epley's manoeuvre (EM) resolves posterior canal benign paroxysmal positional vertigo (PC-BPPV), both effectively and rapidly.

Impact

In the short term, EM is a simple and effective procedure for patients suffering from PC-BPPV.

Aims

Abnormal endolymph flow in the semicircular canals caused by misplaced otoconia can lead to PC-BPPV, a condition associated with position-dependent vertigo and nystagmus. EM, a technique involving five successive head positions, is considered a well-known treatment option for PC-BPPV. However, methodologically rigorous evidence for the extent of its efficacy is limited, with some suggestions that the longer-term impact of treatment may be overestimated, as PC-BPPV can resolve spontaneously. This study aimed to evaluate the efficacy of EM for the treatment of PC-BPPV, 24h after applying the manoeuvre.

Methods

Patients: 67 patients from a dizziness clinic ($n = 57$) and a neurologist's practice ($n = 10$) in Germany.

Inclusion criteria:

- Short-lasting vertigo (<1min) precipitated by head position changes;
- Nystagmus beating towards the undermost ear in one of the lateral head-hanging positions of the Dix–Hallpike (DHP) manoeuvre, lasting <30s;
- Brief latency between head positioning and the onset of nystagmus.

Exclusion criteria:

- Bilateral benign paroxysmal positional vertigo (BPPV);
- Involvement of the horizontal or anterior semicircular labyrinthine canals;
- Previous treatment with EM.

Groups:

- EM on the affected side ($n = 36$);
- Sham procedure: EM for the non-affected side ($n = 31$).

DHP testing and EM were repeated during one treatment session, until nystagmus and vertigo could no longer be elicited. Patients in the EM group were treated by up to three manoeuvres; patients in the sham group were treated with a similar number of manoeuvres as the previous patient in the EM group.

Randomization, allocation concealment, and blinding: A computer-generated randomization code list was used. Sealed, coded envelopes were opened, after written informed consent was obtained. Outcome assessment at 24h was blinded for treatment allocation.

Follow-up measurements: DHP testing was performed by an investigator blinded to previous treatment. Subjective outcome was assessed by a telephone interview at 1wk and 1mo.

Primary outcome: Treatment success at 24h (defined as absence of positional vertigo and nystagmus on DHP performed twice).

Secondary outcomes: Treatment success of controls when EM was performed correctly (for the affected side) after the initial assessment at 24h, patient-reported symptoms at 1wk and 1mo, adverse effects.

Results

Table 28.5 Summary of result

| | EM (n = 35) | Sham (n = 31) | p |
|--------------------------|-------------|---------------|--------|
| Free of nystagmus at 24h | 28 (80%) | 3 (10%) | <0.001 |
| Free of BPPV at 24h | 28 (80%) | 4 (13%) | <0.001 |
| Free of BPPV at 1wk | 33/35 (94%) | 22/27 (82%) | ns |
| Free of BPPV at 4wk | 30/35 (86%) | 22/26 (85%) | ns |
| Required only 1 EM | 15 (43%) | 15 (48%) | ns |

- 27/28 (96%) of the EM group who were successfully treated by EM to the affected side remained BPPV-free during F/U (see Table 28.5);
- 26/28 (93%) of patients in the sham group reported resolution of symptoms 1d after receiving EM for the affected side.

Discussion

This trial demonstrated that treatment of PC-BPPV with EM is more effective than a sham procedure at 24h post-treatment. At 1wk and 1mo post-treatment, patients treated by EM had similar symptoms (based on subjective outcome assessment by telephone interview) to those receiving the sham procedure. However, this finding should be interpreted with caution, as all patients who had a positive DHP test at the initial assessment (24h after randomization) received up to three EMs for the affected side, and 93% of patients in the sham group reported resolution of symptoms 1d after receiving such EM for the affected side.

Chronic dizziness: booklet-based vestibular rehabilitation

Clinical and cost effectiveness of booklet based vestibular rehabilitation for chronic dizziness in primary care: single blind, parallel group, pragmatic, randomised controlled trial.

AUTHORS: Yardley L, Barker F, Muller I et al.

REFERENCE: *BMJ* (2012) 344:e2237.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

At 1y, booklet-based vestibular rehabilitation (VR) improved patient-reported dizziness symptoms, compared to routine care, in patients suffering from chronic dizziness not attributable to non-vestibular causes. This treatment also appeared to be cost-effective.

Impact

Booklet-based VR for chronic dizziness is a simple and cost-effective strategy for patients with chronic dizziness in 1° care.

Aims

Persistent dizziness is a commonly encountered complaint in 1° care. For cases caused by vestibular dysfunction, VR or 'balance retraining' through a series of graded exercises has been thought to result in partial or complete resolution of symptoms and balance problems. Access to VR usually involves referral to 2° care for assessment, and locating suitable trained VR therapists can be challenging. Alternative models of VR that can deliver prompt and cost-effective treatment to a larger proportion of patients are therefore warranted. This study aimed to determine whether booklet-based VR, with and without expert telephone support, was an efficacious and cost-effective alternative to routine care in 1° care.

Methods

Patients: 337 patients from 35 GPs across England.

Inclusion criteria:

- Dizziness during the past 2y;
- Age >18y.

Exclusion criteria:

- Dizziness attributed to non-vestibular causes;
- Dizziness not aggravated by rapid head movements;
- Contraindication to treatment by VR.

Groups:

- Booklet-based VR and telephone support by vestibular therapist ($n = 112$);
- Booklet-based VR only ($n = 113$);
- Routine medical care ($n = 112$).

Randomization, allocation concealment, and blinding: An independent randomization service allocated patients to one of the three interventions. Randomization was stratified for symptom severity. Participants, therapists, and the trial administrator were not blinded to treatment allocation, but the researchers who assessed and analysed outcomes were.

Follow-up measurements: Patient-reported questionnaires at 12wk and 1y.

Primary outcome: Total scores on the vertigo symptom scale-short (VSS-S) form at 12wk.

Secondary outcomes: Total scores on the VSS-S form at 1y, subjective improvement of dizziness, EQ-5D, and costs.

Results

Table 28.6 Summary of result

| Outcomes | | Routine care | VR and tel. support | VR only | <i>p</i> (1 vs 2) | <i>p</i> (1 vs 3) |
|------------------------|----------|--------------|---------------------|---------|-------------------|-------------------|
| VSS-S form | Baseline | 13.7 | 12.9 | 12.2 | | |
| | 12wk | 10.5 | 8.3 | 9.1 | 0.06 | 0.53 |
| | 1y | 11.0 | 8.3 | 7.6 | 0.01 | 0.01 |
| Subjective improvement | 12wk | 40/107 | 57/100 | 62/105 | 0.005 | 0.002 |
| | 1y | 47/99 | 66/95 | 60/100 | 0.002 | 0.09 |

- At 12wk, total scores on VSS-S were similar. At 1y, both VR groups showed greater improvement in VSS-S total scores than the routine care group (see Table 28.6);
- Patients in both VR groups reported subjective improvement more often at both 12wk and 1y;
- Of both VR treatments, booklet-based VR with telephone support was more cost-effective.

Discussion

This methodologically rigorous RCT showed that booklet-based VR, both with and without telephone support, improves symptoms, decreases handicap related to dizziness, and is cost-effective at 1y F/U.

Problems

- A limitation of this trial was the low response rate—fewer than 10% of invited patients participated in the trial. Although ~75% of the non-participants stated they were no longer dizzy, this low participation rate may limit the generalizability of the trial findings.

Acute rhinosinusitis: antibiotics

Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data.

AUTHORS: Young J, De Sutter A, Merenstein D *et al.*

REFERENCE: *Lancet* (2008) **371**, 908–14.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

This IPD meta-analysis showed that antibiotics are not beneficial in adults with clinically diagnosed acute rhinosinusitis, even if a patient reports symptoms for longer than 7–10d. No clinical signs and symptoms were identified to differentiate between those who do and those who do not benefit from antibiotics.

Impact

A no antibiotic or delayed antibiotic strategy is recommended for patients with uncomplicated acute rhinosinusitis.

Aims

Acute rhinosinusitis is a common reason for health-care consultation and antibiotic prescribing in adults. Previous RCTs showed antibiotics to be of limited benefit for patients with uncomplicated disease. It is unknown whether clinical signs and symptoms can be used to differentiate between patients who may benefit more or less from antibiotics. This IPD meta-analysis assessed whether common clinical signs, symptoms, and patient characteristics could be used to identify a subgroup of adult patients with clinically diagnosed acute rhinosinusitis who would benefit from antibiotic treatment.

Methods

Literature search using the Cochrane Library, Medline, and EMBASE to identify all relevant RCTs. 1° investigators of eligible trials were asked to provide raw data.

Inclusion criteria:

- Placebo-controlled RCTs of high methodological quality;
- Participants aged ≥ 12 y with rhinosinusitis-like complaints.

Outcome:

- Proportion of patients cured at the primary endpoint of the trial.

Effect modifiers included in the IPD meta-analysis: Any sign, symptom, or specific patient characteristic recorded in at least four trials, e.g. age, duration of symptoms, purulent nasal discharge, and temperature.

Results

- IPD available for nine of ten eligible trials;
- Adults treated with antibiotics were cured of symptoms more often than those treated with placebo: OR 1.37 (95% CI 1.13–1.66). The mean NNT for 10,000 simulated new patients was 15 (95% CI 7–190 [harm]);
- A meta-analysis of aggregate risk differences for these trials gave a mean NNT of 14 (95% CI 9–30);
- Patients with purulent nasal discharge in the pharynx took longer to cure and were more likely to benefit from antibiotics than other patients. The mean NNT for 10,000 simulated new patients was 8 (95% CI 4–47 [harm]);
- Patients who were older, reported symptoms for at least 6d, or reported more severe symptoms took longer to cure but were no more likely to benefit from antibiotics, as compared to other patients.

Discussion

This IPD meta-analysis showed that the absolute effect of treatment with antibiotics, compared to placebo, was small (NNT = 15). Antibiotics were most beneficial in patients with purulent discharge in the pharynx (NNT = 8). This result should be interpreted with some caution, as it was obtained from an analysis of data from only five of the ten trials considered (1,269 patients; 32% had purulent discharge in the pharynx). Moreover, the absolute benefit from antibiotics reported in this study is too small to justify antibiotic treatment in all patients with clinically diagnosed acute rhinosinusitis presenting with purulent discharge in the pharynx. The findings support current clinical guidance, suggesting a no antibiotic or delayed antibiotic strategy for patients with uncomplicated acute rhinosinusitis.

Recurrent upper respiratory tract infections in children: adenoidectomy

Effectiveness of adenoidectomy in children with recurrent upper respiratory tract infections: open randomised controlled trial.

AUTHORS: Van den Aardweg MTA, Boonacker CWB, Rovers MM *et al.*

REFERENCE: *BMJ* (2011) 343:d5154.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Immediate adenoidectomy conferred no clinical benefit over watchful waiting in children with recurrent URTIs. Prevalence of URTIs decreased equally in children receiving immediate adenoidectomy and those allocated to watchful waiting.

Impact

Children suffering from recurrent URTIs are best managed by a strategy of initial observation.

Aims

Adenoidectomy is one of the most frequently performed surgical procedures in children in Western countries. Indications include otitis media, upper airway obstruction, and recurrent URTIs. URTIs, presenting as recurrent nasal discharge, with or without nasal congestion, are very common in children, and an important subset are referred to 2° care. The evidence on the effectiveness of adenoidectomy in this specific group is scarce. This study aimed to assess the effectiveness of adenoidectomy in children with recurrent URTIs.

Methods

Patients: 111 children from ENT departments of 11 general and two academic hospitals in The Netherlands.

Inclusion criteria:

- Selected for adenoidectomy for recurrent URTIs;
- Age 1–6y.

Exclusion criteria:

- Previous adenoidectomy or adenotonsillectomy;
- Grommets in place or indication for grommet insertion;
- Children with Down's syndrome or craniofacial malformations.

Groups:

- Adenoidectomy with/without myringotomy within 6wk ($n = 54$);
- Watchful waiting ($n = 57$).

Parents, GPs, and ENT surgeons of the participating children were encouraged to manage URTIs during F/U, according to their regular practice.

Randomization, allocation concealment, and blinding: In this open-label trial, a computerized minimization strategy was used, including age (<2 and $\geq 2y$) and hospital. Treatment allocation was concealed, until informed consent was obtained and the child was included in the trial.

Follow-up measurements: During 2y F/U, parents kept a daily symptom diary and measured their child's temperature daily with a validated tympanic membrane thermometer. Home visits by the study physician were scheduled at 3, 6, 12, 18, and 24mo.

Primary outcome: Number of URTIs per person-year defined as ≥ 2 of the following: fever (temperature of $>38^{\circ}\text{C}$, as measured by the tympanic thermometer), diary-scored symptoms of nasal stuffiness or mouth breathing, nasal discharge, sore throat, or cough.

Secondary outcomes: Days with URTI per person-year, incidences of mild and severe URTI, and HRQOL.

Results

- Incidence of URTI episodes during F/U in the adenoidectomy and WW groups was 7.91 and 7.84 per person-year, respectively;
- Proportions of children with URTI (prevalence per week) (see Fig. 28.1).
- No differences observed between the two groups in the incidence of mild and severe URTI episodes;
- HRQOL was similar across the two groups.

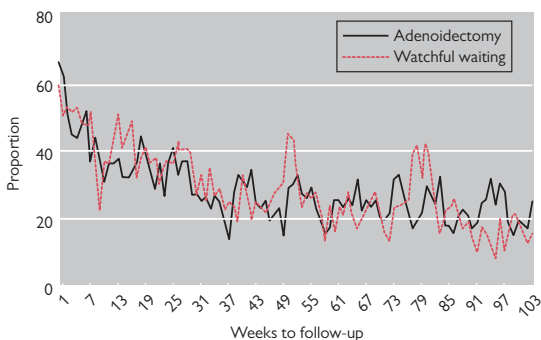


Fig. 28.1 Proportions of children with URTI.

Discussion

Immediate adenoidectomy offered no clinically significant benefit over watchful waiting in children selected for surgery because of recurrent URTIs. An economic evaluation of this study showed that immediate surgery resulted in an increase in costs, compared to initial observation (*JAMA Otolaryngol Head Neck Surg* (2013) **139**, 129–33). Although the study was unblinded, due to the nature of the intervention, information bias was avoided by the use of an electronic device that was built in the validated tympanic membrane thermometers. This device stored the date and first temperature measurement of each day. Forty percent of children in the initial watchful waiting group underwent surgery during the course of the trial, while 19% in the surgical group had additional surgery. No differences were found in baseline variables or in the number of URTIs during the first year of F/U between those children in the control group who did and those who did not 'cross over'. The results of the per-protocol and as-treated analyses did not differ from the ITT analysis regarding URTIs during F/U.

Chronic rhinosinusitis with moderate to severe nasal polyposis: oral steroids followed by intranasal steroids

Treatment of chronic rhinosinusitis with nasal polyposis with oral steroids followed by topical steroids.

AUTHORS: Vaidyanathan S, Barnes M, Williamson P et al.

REFERENCE: *Ann Intern Med* (2011) 154, 293–302.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Oral steroid followed by intranasal steroid was more effective at 6mo than intranasal steroid alone in decreasing polyp size and improving olfaction in patients with chronic rhinosinusitis with moderate to severe nasal polyposis.

Impact

Oral steroid followed by intranasal steroid is recommended in patients with chronic rhinosinusitis (CRS) with moderate to severe nasal polyposis.

Aims

CRS affects 10% of the UK adult population. An important group of these patients suffer from nasal polyps (CRSwNP), causing symptoms such as nasal obstruction and discharge, hyposmia, and facial pain/pressure. This condition has a significant impact on patients' QoL. Current evidence regarding the effectiveness of treatment options for CRSwNP is scarce. It had been hypothesized that intranasal therapies alone did not penetrate into the sinus openings sufficiently and thus would not improve sinus drainage. This trial aimed to assess whether initial therapy with oral steroid followed by intranasal steroid would lead to a greater and sustained benefit in patients with CRS and nasal polyps.

Methods

Patients: 60 patients from an ENT clinic in Tayside in Scotland.

Inclusion criteria:

- Non-smoking patients with CRSwNP (bilateral moderate to large nasal polyps on nasendoscopy);
- Age >18y.

Exclusion criteria:

- Oral steroid treatment in previous 3mo;
- Sinus surgery in previous year;
- Recent URTI;
- Mechanical airway obstruction of >50% due to septal deviation.

Groups:

- Prednisolone 25mg daily for 2wk ($n = 30$);
- Placebo ($n = 30$).

After the first 2wk, all participants received fluticasone nasal drops for 8wk, followed by fluticasone nasal spray for 18wk. No other rhinitis medication or antibiotics permitted during the study.

Randomization, allocation concealment, and blinding: A computer-generated random allocation sequence using block randomization. A random sequence list was produced by an independent off-site clinical trials pharmacist who also masked and blinded prednisolone and identical placebo. Tablets were distributed in sealed opaque envelopes at the research unit, in sequential order, by a technician who was not directly involved with the study.

Follow-up measurements: Main efficacy and safety outcomes were measured at baseline and after each treatment period at 2, 10, and 28wk. Standard video sequences of nasendoscopic investigation were stored on a computer and viewed by two independent observers who were blinded to patient treatment and sequence. Secondary outcome measures included a 100mm hyposmia VAS scale, the Pocket Smell Test, and subjective symptom reporting.

Primary outcome: Nasendoscopic polyp grading.

Secondary outcomes: Olfaction, nasal airflow, QoL, safety.

Results

- Polyp grade (in units) from baseline decreased more in the prednisolone group than in the placebo group at 2, 10, and 28wk: 2.1 vs 0.1, 2.5 vs 1.6, and 1.9 vs 1.5, respectively;
- Hyposmia scores (in mm) improved more in the prednisolone group than in the placebo at 2, 10, and 28wk: 31.1 vs 1.4, 21.4 vs 15.0, and 19.4 vs 11.8, respectively;
- At 2wk, total nasal symptom scores, QoL, and peak nasal inspiratory flow significantly favoured prednisolone. However, no statistical significant differences between groups were observed during further F/U;
- No serious adverse events were reported. Basal and dynamic adrenal function was suppressed by oral prednisolone but recovered after the switch to nasal drops.

Discussion

This well-designed trial demonstrated that oral steroids (prednisolone 25mg daily) for 2wk followed by intranasal steroids leads to a significant and sustained improvement in polyp size and olfaction, compared with placebo, in patients with CRS with moderate to severe nasal polyposis. Although both basal and dynamic adrenal function were suppressed by oral prednisolone at 2wk, no significant residual adrenal suppression was observed at 10 and 28wk F/U.

Problems

- A single centre, which only included patients with moderate to severe nasal polyposis. The findings are therefore only applicable to patients with more severe disease. Further studies are necessary to establish whether patients with milder disease would also benefit.

Acute sore throats in children: penicillin

Penicillin for acute sore throat in children.

AUTHORS: Zwart S, Rovers MM, de Melker RA *et al.*

REFERENCE: *BMJ* (2003) 327, 1324–7.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Penicillin treatment has no benefit in reducing the average symptom duration in acute sore throat but may reduce streptococcal sequelae. Seven eligible children need to be treated to prevent a worsening illness in one child.

Impact

This study confirms recommendations that most children with acute sore throat do not benefit from antibiotic treatment. Their prescription can be delayed for worsening symptoms or for signs of peritonsillar abscess formation.

Aims

~15–30% of cases of pharyngitis presented to a doctor are caused by group A β -haemolytic *Streptococcus* (GABHS). Although penicillin had been demonstrated to be effective in adult patients with GABHS pharyngitis, there was limited evidence for its effectiveness in children. This study aimed to assess the effectiveness of penicillin treatment for 3d and 1wk, as compared with placebo, in resolving symptoms in children with acute sore throat.

Methods

Patients: 156 children from 43 GPs in The Netherlands.

Inclusion criteria:

- Age 4–15y;
- Acute sore throat (symptoms for <7d) and at least two of the four Centor criteria (fever, absence of cough, swollen and tender anterior cervical lymph nodes, tonsillar exudates).

Exclusion criteria:

- Children with an imminent peritonsillar abscess, scarlet fever, intercurrent disease requiring antibiotics, and penicillin intolerance.

Groups:

- Penicillin V (250mg three daily for 4–10 year olds/500mg three daily for 10–15 year olds) for 1wk ($n = 46$);
- Penicillin V for 3d, followed by placebo for 4d ($n = 54$);
- Placebo for 1wk ($n = 56$).

Randomization, allocation concealment, and blinding: Random assignment, according to a computer-generated list that was blinded to both patients and doctors. An independent pharmacist filled and numbered the medication trays. Participating doctors received medication trays from the study coordinator, to be used in the numbered order.

Follow-up measurements: Symptom diary kept by patients or parents daily for 2wk, body temperature, usage of analgesia. Children examined at 2wk by their GP. Throat swabs taken after randomization and at 2wk. Telephone interviews at 2, 4, and 6mo.

Primary outcome: Symptom duration (number of days until pain had resolved).

Secondary outcomes: Mean usage of analgesia, absence from school, development of streptococcal sequelae such as peritonsillar abscess, eradication of the initial pathogen after 2wk, and recurrent episodes of sore throat over the next 6mo.

Results

Table 28.7 Summary of result

| | Placebo | Penicillin for 3d | Penicillin for 1wk |
|---|---------------|-------------------|--------------------|
| Mean duration of sore throat (d) (95% CI) | 3.8 (3.3–4.3) | 4.6 (4.0–5.2) | 3.8 (3.2–4.4) |
| Mean absence from school (d) (95% CI) | 2.4 (1.8–3.0) | 2.3 (1.7–2.9) | 2.8 (2.2–3.5) |
| Mean consumption of pain killers (d) (95% CI) | 1.4 (1.0–1.8) | 1.4 (1.0–1.9) | 1.1 (0.7–1.6) |

- A total of 11 children developed streptococcal sequelae—nine had an imminent peritonsillar abscess, one scarlet fever, and one impetigo. Of those, one child was allocated to penicillin for 7d, two to penicillin for 3d, and eight to placebo, resulting in an incidence rate ratio of 0.15 (95% CI 0.02–1.2) and 0.26 (95% CI 0.06–1.2), respectively. After unblinding, all 11 children received antibiotic treatment and did recover uneventfully, without referral to a hospital. (See Table 28.7.)

Discussion

This well-designed RCT found no significant benefit of antibiotics over placebo, in terms of symptom duration, in children suffering from acute sore throat. The findings were similar for those children with throat swab-proven GABHS infection. The trial did suggest that antibiotic treatment may reduce the risk of streptococcal sequelae, but it lacked the power to provide any firmer conclusions. All patients with these sequelae subsequently improved with penicillin, suggesting it would be appropriate to adopt a watchful waiting strategy for those children whose symptoms do not resolve or deteriorate. A useful commentary followed this paper and calculated the NNT as 7 children (*BMJ* (2003) 327, 1327–8).

Childhood obstructive sleep apnoea: adenotonsillectomy

A randomized trial of adenotonsillectomy for childhood sleep apnea.

AUTHORS: Marcus CL, Moore RH, Rosen CL *et al.*

REFERENCE: *N Engl J Med* (2013) **368**, 2366–76.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

In school-age children with OSA, early adenotonsillectomy is effective in reducing symptoms and improving behaviour, QoL, and polysomnographic findings. The operation had no significant effect on cognitive function.

Impact

Adenotonsillectomy has beneficial effects in school-age children with OSA. However, a period of initial observation with medical management seems a valid treatment option, as polysomnographic findings of a large proportion of children in the non-surgical group normalized by 7mo.

Aims

OSA may significantly impair daily functioning and cause cognitive and behavioural deficits in children. Since adenotonsillar hypertrophy is the prime risk factor for childhood OSA, adenotonsillectomy is the treatment of choice for most of these children. However, thus far, no controlled studies had evaluated this surgical procedure. This study aimed to assess the effectiveness of adenotonsillectomy, as compared to watchful waiting with supportive care, in school-age children with OSA.

Methods

Patients: 464 children at seven academic sleep centres in the USA.

Inclusion criteria:

- Age 5–9y;
- Selected for adenotonsillectomy because of OSA, defined as Apnoea/Hypopnoea Index (AHI) score of ≥ 2 events per hour or an Obstructive Apnoea Index (OAI) score of ≥ 1 events per hour, without prolonged oxyhaemoglobin desaturation.

Exclusion criteria:

- AHI score of >30 events per hour and/or OAI score of ≥ 20 events per hour and/or arterial oxyhaemoglobin saturation of $<90\%$ for $\geq 2\%$ or more of the total sleep time;
- Recurrent tonsillitis, a z score (based on the BMI) of ≥ 3 , medication for ADHD.

Groups:

- Adenotonsillectomy within 4wk after randomization ($n = 226$);*
- Watchful waiting ($n = 227$).

Medical conditions that could exacerbate OSA, such as allergies or poorly controlled asthma, were treated, as needed.

* Eleven of the 464 children were excluded, owing to site withdrawal.

Randomization, allocation concealment, and blinding: Single-blind study—children and parents unblinded, but sleep physicians and staff performing neuropsychological testing blinded. Randomization stratified by site, age, race, and body weight, using a web-based procedure. Clinic sites did not have access to the randomization list.

Follow-up measurements: At baseline and 7mo. Polysomnographic, cognitive, and behavioural testing, and other clinical and laboratory evaluations performed. Caregivers completed questionnaires.

Primary outcome: Change in the attention and executive function score on the Developmental Neuropsychological Assessment (NEPSY).

Secondary outcomes: Caregiver and teacher ratings of behaviour (Conners' Rating Scale and BRIEF), symptoms of OSA, sleepiness, QoL, and polysomnographic indexes.

Results

Table 28.8 Summary of results

| | ATE | | WW | | <i>p</i> |
|--|--------------|-------------|--------------|--------------|----------|
| | Baseline | Change | Baseline | Change | |
| NEPSY attention and executive function score | 101.1 ± 14.6 | 5.1 ± 13.4 | 101.5 ± 15.9 | 7.1 ± 13.3 | 0.16 |
| Conners' Rating Scale, caregivers | 52.6 ± 11.7 | −0.2 ± 9.4 | 52.5 ± 11.6 | −2.9 ± 9.9 | 0.01 |
| Conners' Rating Scale, teachers | 55.1 ± 12.8 | −1.5 ± 10.7 | 56.4 ± 14.4 | −4.9 ± 12.9 | 0.04 |
| BRIEF score, caregivers | 50.1 ± 11.5 | 0.4 ± 8.8 | 50.1 ± 11.2 | −3.3 ± 8.5 | <0.001 |
| BRIEF score, teachers | 56.4 ± 11.7 | −1.0 ± 11.2 | 57.2 ± 14.1 | −3.1 ± 12.6 | 0.22 |
| AHI (no. of events/h) | | | | | |
| Median | 4.5 | −1.6 | 4.8 | −3.5 | <0.001 |
| IQR | 2.5–8.9 | −3.7 to 0.5 | 2.7–8.8 | −7.1 to −1.8 | |

- Children undergoing early adenotonsillectomy had greater improvement of symptoms of OSA and QoL, compared to those allocated to watchful waiting (see Table 28.8);
- Irrespective of the assigned treatment, polysomnographic findings normalized less frequently in black vs children of other ethnic origin, obese vs non-obese children, and those with baseline AHI score above the median vs AHI score below the median;
- Fifteen serious adverse events occurred: nine in the watchful waiting group and six in the surgical group; eight perioperative complications observed (including tonsillar bleeding in four children).

Discussion

Although this high-quality trial showed that early adenotonsillectomy reduced symptoms and improved behaviour, QoL, and polysomnographic findings in children with OSA, early surgery did not improve attention or executive functioning significantly. Remarkably, almost 50% of children allocated to watchful waiting had normalization of their AHI score at 7mo, suggesting a period of observation to be justified in these children.

Severe obstructive sleep apnoea: surgery vs positive airway pressure

Surgery vs ventilation in adult severe obstructive sleep apnea syndrome.

AUTHORS: Vicini C, Dallan I, Campanini A *et al.*

REFERENCE: *Am J Otolaryngol* (2010) 31, 14–20.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Patients suffering from severe obstructive sleep apnoea hypopnoea syndrome (OSAHS) reported substantial improvement of symptoms at 1y with maxillomandibular advancement (MMA) surgery. The same improvement was seen with autotitrating positive airway pressure (APAP) ventilatory treatment.

Impact

APAP and MMA are equally effective in patients with severe OSAHS. In patients failing to improve with ventilatory treatment, surgery is an option. However, the risk of complications of surgery should be carefully balanced against its benefits.

Aims

Over the past decades, the prevalence of OSAHS has increased considerably, along with the widespread increase in obesity. OSAHS not only has a significant impact on daily activities and QoL, but also increases the risk of CV disease. Recent studies showed CPAP to be equally effective as APAP in OSAHS. A major issue of ventilation therapy is non-compliance and adverse effects, including nasal congestion, dry mucosal tissue irritation, and mask discomfort. However, the role of surgery in OSAHS is debatable, especially in patients who are severely affected (i.e. AHI >30). This study aimed to assess the effectiveness of surgery (MMA) in patients with severe OSAHS.

Methods

Patients: 50 patients from an ENT/oral surgery unit in Forlì in Italy.

Inclusion criteria:

- Severe OSAHS (AHI >30).

Exclusion criteria:

- Contraindication for surgery, e.g. pre-existing medical conditions that could increase the risk of surgery;
- Contraindication for APAP, e.g. COPD, heart failure.

Groups:

- MMA ($n = 25$);
- APAP ($n = 25$).

Follow-up measurements: Post-operative measurements included severity of OSAHS, daytime sleepiness using the Epworth Sleepiness Scale (ESS), and the degree of subjective overall satisfaction using VAS.

Primary outcome: Change in AHI and ESS.

Secondary outcomes: Degree of subjective satisfaction.

Results

- Patients who underwent MMA had similar AHI and ESS improvement, as compared to those allocated APAP, at post-operative F/U measurements ($p = 0.21$ and $p = 0.20$, respectively);
- The degree of subjective satisfaction after treatment was comparable between the MMA and APAP group;
- All patients had transient paraesthesiae in the infraorbital and mandibular regions, with seven reporting persistent, non-disturbing paraesthesiae around the chin. Six patients reported a slight-to-minimal malocclusion, and an orthodontic correction was required in one patient.

Discussion

This RCT showed MMA to be equally effective as APAP in patients with severe OSAHS. However, with a number of study limitations, it remains unclear whether the authors concluded surgery to be superior or non-inferior to APAP. The findings of the current study should therefore be interpreted with caution. Further large—preferably multicentre and well-designed—RCTs are necessary to draw more robust conclusions on the role of surgery in patients with severe OSAHS.

Problems

- Relatively small number of patients, and the authors did not report on their sample size calculation.
- No details on the method of randomization, concealment of allocation, and blinding (of outcome assessment) were provided.

Laryngopharyngeal reflux: proton pump inhibitors

Double-blind, placebo-controlled trial with single-dose pantoprazole for laryngopharyngeal reflux.

AUTHORS: Wo JM, Koopman J, Harrell SP et al.

REFERENCE: *Am J Gastroenterol* (2006) **101**, 1972–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Pantoprazole did not improve symptom relief more than placebo in patients suffering from laryngeal complaints and a positive triple-sensor pH test.

Impact

PPIs should not be routinely prescribed in patients suffering from laryngopharyngeal reflux (LPR) without typical symptoms of GORD.

Aims

LPR may cause laryngeal symptoms such as hoarseness, cough, and throat discomfort. Suppression of hypopharyngeal acid reflux with PPIs had been hypothesized to improve these symptoms. Previous trials of PPI for LPR reported conflicting results and generally did include positive pH testing as an entry criterion. The current RCT aimed to determine the effectiveness of single daily-dose PPI in the treatment of pH-proven LPR.

Methods

Patients: 39 patients from ENT outpatient clinics at the University of Louisville in the USA.

Inclusion criteria:

- Laryngeal complaints for ≥ 3 d/wk in the past 2mo;
- Confirmation of diagnosis by laryngeal exam and a positive pH test of the hypopharynx or distal oesophagus.

Exclusion criteria:

- Previous treatment for LPR or GORD, previous endoscopic or surgical antireflux procedure, previous gastric surgery;
- Known gastroparesis, connective tissue disorder.

Groups:

- Pantoprazole 40mg od for 12wk ($n = 20$);
- Placebo daily for 12wk ($n = 19$).

Antacids were allowed only as needed for GORD symptoms, and not for laryngeal complaints.

Randomization, allocation concealment, and blinding: Block randomization list generated by a third party not involved in the trial. The study coordinator allocated each patient to the next available number from the assignment list. Participants and all study personnel were blinded to the randomization. Placebo and pantoprazole tablets were of identical appearance.

Follow-up measurements: Study visits at midpoint and end of 12wk treatment period. At the end visit, triple-sensor pH monitoring was repeated. During the 12wk treatment period and 4wk F/U off treatment, participants filled out weekly symptom diaries.

Primary outcome: Total laryngeal symptom score, as reported by patients.

Secondary outcome: Global assessment of patient-reported laryngeal symptoms at end of treatment period.

Results

- Weekly (total) laryngeal symptoms (scores) improved in both groups during the 12wk treatment period, with no significant differences between those treated with pantoprazole or placebo;
- Patients receiving pantoprazole had higher total laryngeal symptom scores during the 4wk off-treatment F/U period than those allocated to placebo;
- At 12wk, the proportion of patients reporting adequate laryngeal symptom relief was similar in the pantoprazole and placebo group: 40% and 42%, respectively;
- Pre- and post-treatment hypopharyngeal reflux episodes did not differ between the treatment groups.

Discussion

This RCT found no benefit of pantoprazole in patients with newly diagnosed LPR, as confirmed by a positive triple-sensor pH test. The finding that patients treated with PPI had higher laryngeal symptom scores during the 4wk off treatment, compared to those receiving placebo, suggest rebound acid production and reflux after PPI use. An earlier RCT of 30 participants with ≥ 4 episodes of laryngeal reflux at 24h dual-channel pH probe testing showed omeprazole 40 mg bd to be more effective than placebo in improving hoarseness and throat clearing, but not in overall laryngeal symptoms (*Laryngoscope* (2001) 111, 2147–51). These studies suggest that PPIs should therefore not be routinely prescribed in patients suffering from LPR without typical symptoms of GORD.

Plastic and reconstructive surgery

- Introduction 796
- Malignant melanoma: excision margins 798
- Melanoma: lymph node status 800
- Facial basal cell carcinoma: type of resection 802
- Hypertrophic burn scars 804
- Vacuum-assisted closure 806
- Breast augmentation: type of implant 808
- Breast reduction: drainage 810
- Flexor tendon rehabilitation 812

Introduction

The current misinterpretation that the term ‘plastic surgery’ arose from making people look plastic or filling their breasts with plastic could not be further from the truth. The term ‘plastic’ was used in relation to plastic surgery long before the hydrocarbon-based material plastics were ever created. Derived from the Greek ‘plastikos’, the word means ‘fit for moulding’—an apt description of plastic surgery’s aim in using the body (or parts of it) to mould and reconstruct in the most functional and aesthetic way possible. Honorably, the parts utilized are often considered discardable and worthless from often overlooked bits of the body; this has permitted the specialty to gain in prominence and importance.

In plastic and reconstructive surgery, innovation and creativity have been foremost, with (occasionally) science and evidence following. Unlike for a number of other specialties, the advances in plastic surgery have largely come from imagination, innovations, and trial and error, rather than from scientific trials. Somewhat more than for the rest of surgery, in plastics (where the art and craft of each particular surgeon counts immeasurably), RCTs of technique have failed to be generated, as requesting plastic surgeons to strictly follow a particular technique is akin to asking an artist to paint by numbers. Furthermore, assessing the outcome of surgery, particularly of aesthetic procedures, is practically impossible, given that ‘beauty is in the eye of the beholder’.

Fortunately, plastic surgeons are, by nature, critical of their own and others’ results (especially of others) and seek constant perfection and reassurance. As is proven by this chapter, the era of evidence is finally among us, and scientific trials are now being performed in plastic surgery, albeit to answer the relatively minor—but no less important—questions.



Malignant melanoma: excision margins

Thin stage I primary cutaneous malignant melanoma: comparison of excision with margins of 1 or 3 cm.

AUTHORS: Veronesi U, Cascinelli N, Adamus J *et al.*

REFERENCE: *N Engl J Med* (1988) **318**, 1159–62.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Narrow surgical lateral excision margins (1cm) are as effective as wide excision margins (3cm) in patients with melanomas of up to 1mm in thickness.

Impact

Current guidelines, based on this RCT, suggest that, for patients with thin melanomas (<1mm thick), a surgical margin of 1cm is appropriate. This has resulted in a significant decrease in the number of cutaneous malignant melanoma patients requiring skin grafts as a result of the excision of their thin tumour. Subsequent studies have led guidelines to recommend >1cm excision in melanomas of ≥ 2 mm in depth.

Aims

Wide excision, with margins of 3–5cm, had been common practice for decades, despite this not being an evidence-based approach. Case reports had suggested that narrower margins were satisfactory in thin melanomas; however, consensus had not been reached as to the optimal size of the margin or the thickness of tumours that were amenable to such conservative approaches. This study aimed to compare outcomes following excision of thin, stage I, 1° cutaneous malignant melanomas using margins of either 1 or 3cm.

Methods

Patients: 612 patients at multiple international centres.

Inclusion criteria: Clinical stage I melanoma of ≤ 2 mm thickness.

Exclusion criteria:

- Melanomas on the face, fingers, or toes;
- Multiple 1° lesions or satellite lesions;
- Age >65y.

Groups:

- Narrow (1cm) excision margins ($n = 305$);
- Wide (3cm) excision margins ($n = 307$).

Evaluations: F/U every 2mo for 2y, then every 3mo from third to fifth year.

Primary endpoints: DFS and overall survival.

Secondary endpoints: Local and regional recurrence, and distant metastases, according to site of first relapse.

Results

Table 29.1 Summary of results

| Primary endpoint | Narrow | Wide | <i>p</i> |
|------------------|--------|------|----------|
| DFS (at 55mo) | 96.8% | 96% | 0.7 |

Discussion

For patients with thin melanomas (up to 1mm thickness), a narrow excision margin of 1cm was as effective a treatment as a wider margin of 3cm at body sites, excluding the face, fingers, and toes. Prior to this study, it was standard clinical practice to take wider margins of 3cm in patients with thin melanomas. This study did not satisfactorily clarify the optimal excision margin for melanomas of thickness between 1 and 2mm. A more recent multicentre RCT of 900 patients by Thomas *et al.* (*N Engl J Med* (2004) **350**, 757–67) found a 1cm excision margin to have a greater risk of locoregional recurrence than a 3cm margin in malignant melanomas of ≥ 2 mm depth; however, there was no significant difference in survival at 60mo. There remains no clear evidence for choosing between 2 and 3cm excision margins. (See Table 29.1.)

Problems

- The results of this study suggested that narrow surgical margins (1cm) were as effective as wider margins (3cm) in patients with cutaneous melanoma no thicker than 2mm. However, the first sign of recurrent disease in three individuals within the study was local recurrence; all three patients had melanomas at least 1mm thick and had been treated with a narrow surgical margin of 1cm. Thus, the current British Association of Dermatologists' guidelines recommend that, for melanomas between 1 and 2mm thick, the margin should be a minimum of 1cm, with a discussion of the case in a multidisciplinary team meeting and appropriate counselling of the patient. Many clinicians will take a wider margin with melanomas greater than 1mm thick.
- The F/U for this study was over a 5y period. It is not clear whether outcomes between the two treatment groups would differ beyond this time.
- Although surgical treatment is often a curative intervention for thin cutaneous malignant melanoma, adjuvant therapies for more advanced disease are currently ineffective.

Melanoma: lymph node status

MSLT (**M**ulticentre **S**elective **L**ymphadenectomy **T**rial): Sentinel node biopsy or nodal observation in melanoma.

AUTHORS: Morton D, Thompson J, Cochran A *et al.*

REFERENCE: *N Engl J Med* (2006) 355, 1307–18.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Large randomized trial showing that sentinel node biopsy may confer a survival benefit by permitting earlier lymphadenectomy. This trial also shows the staging reliability of sentinel node biopsy.

Impact

This trial reinforces the role of sentinel node biopsy in the management of melanoma and the need for lymphadenectomy when the biopsy is positive.

Aims

Although resection is usually curative in most patients with clinically localized melanoma of intermediate thickness, metastasis to regional nodes occurs in 15–20%. Regional node metastasis is the most important prognostic factor in early-stage disease; for this reason, some have advocated immediate lymphadenectomy. However, this is not without morbidity, and an overall survival advantage has not been demonstrated in the majority. Sentinel node biopsy is a technique that can be used to help accurately stage melanoma, in order to determine whether more major lymph node resection is necessary. This study aimed to determine the value of sentinel node biopsy and the effects of completion lymphadenectomy on positive biopsies on survival and recurrence.

Methods

Patients: 1,269 patients from multiple centres in the USA, Australia, and Europe.

Inclusion criteria: 1° melanoma (1.2–3.5mm deep) with:

- Clark level 3, with Breslow thickness >1mm;
- Clark level 4–5, with any Breslow thickness.

Groups: Randomized in 60:40 ratio to treatment groups. Both groups had wide excision of the 1° melanoma:

- Observation of lymph nodes, with lymphadenectomy if they became palpable ($n = 500$);
- Sentinel node biopsy, with lymphadenectomy if biopsy was positive ($n = 769$).

Primary endpoint: Survival until death from melanoma.

Secondary endpoints:

- Survival without evidence of recurrence or metastasis (DFS);
- Incidence of nodal metastases and survival once detected.

Follow-up: Every 3mo with examination, chest X-ray, and bloods for first 2y; then every 4mo in y 3; then every 6mo in y 4–5; then annually until y 10. Median F/U 59.8mo.

Results**Table 29.2** Summary of results

| Primary endpoint | Sentinel node | Observation | p |
|--------------------------------------|---------------|-------------|--------|
| Melanoma-specific death | 12.5% | 13.8% | ns |
| Secondary endpoints | | | |
| DFS | 78.3% | 73.1% | 0.009 |
| 5y survival once lymph basin treated | 72.3% | 52.4% | <0.001 |
| Incidence of nodal metastases | 19.4% | 18.5% | ns |

Discussion

This study confirmed the ability of sentinel node biopsy to accurately stage and provide prognostic evaluation of intermediate-level melanomas. Positive sentinel node biopsy and immediate lymphadenectomy increased the 5y survival rate from 52.4% to 72.3%, compared with delayed lymphadenectomy for palpable lymph nodes, and reduced the death rate from 48.7% to 26.2%; it also reduced recurrence. This confirmed the findings of other smaller studies. In those without nodal disease, sentinel node biopsy did not affect survival or recurrence. (See Table 29.2.)

Problems

- Statistically, the results are only valid if the assumption that a positive sentinel node would progress to nodal disease is true.
- The median time to detection of nodal relapse in the observation group was 1.33y.
- This is an interim result; the final results of this study are still pending.

Facial basal cell carcinoma: type of resection

Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face.

AUTHORS: Smeets N, Krekels G, Osterag J et al.

REFERENCE: *Lancet* (2004) **364**, 1766–72.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There is no difference in the recurrence rates of 1° or recurrent basal cell carcinoma (BCC), when treated with either surgical excision or Mohs' micrographic surgery (MMS).

Impact

MMS, which is more costly and time-consuming, can now be safely reserved for those multiply recurrent BCCs, morphoeic BCCs, or indistinct BCCs in particularly anatomically sensitive areas.

Aims

BCC is the commonest skin cancer in Caucasians, with a rising incidence. It rarely metastasizes, but the morbidity (and mortality) from some, particularly if large or incompletely treated, can be significant. There had been a widely held belief that recurrence rates of BCCs were lower when treated by MMS (utilizing a systematic microscopic examination of the tumour site), compared with the more commonly used surgical excision. However, MMS is a more time-consuming, hence more expensive, procedure. This study aimed to identify whether there were subsets of facial BCC in which MMS would be more effective than surgical excision.

Methods

Patients: 565 patients (612 BCCs) from two European centres.

Inclusion criteria: Facial BCC:

- Histologically confirmed BCC;
- At least 1cm in diameter if non-aggressive type, or any size if aggressive type (morphoeic, micronodular, squamous differentiation, infiltrative, trabecular—these account for ~50% of cases);
- Recurrence must be biopsy-proven, any size.

Exclusion criteria: Life expectancy <3y.

Groups: Classified by 1° or recurrent BCC status; 3mm resection margin used for both groups:

- Surgical excision ($n = 204$ 1°; 102 recurrent);
- MMS ($n = 204$ 1°; 102 recurrent).

Primary endpoint: Recurrence of the BCC.

Secondary endpoints:

- Incomplete excision;
- Suboptimal aesthetic results;
- Costs of treatment.

Follow-up: At 6mo and 18mo by researcher for photographs and aesthetic assessment, in addition to normal cancer F/U for recurrence. Mean F/U 2.66y.

Table 29.3 Summary of results

| Primary endpoint | Surgical excision | MMS | p |
|--|----------------------------------|--------------|---------|
| Recurrence | 8 cases | 2 cases | ns |
| Secondary endpoints | | | |
| Incomplete excision | 18% of 1° and 32% of recurrences | No cases | <0.001 |
| Defect size: 1° / recurrent (cm ²) | 4.64/7.78 | 4.06/7.50 | 0.4/0.6 |
| Suboptimal aesthetic | No difference | | ns* |
| Cost (1° tumour) | 216.86 euros | 405.79 euros | <0.001 |

* But 1° tumours had significantly better aesthetic outcome than recurrent ($p = 0.04$).

Results

Discussion

With 50% of BCCs comprising the aggressive type, the average 1° size treated was 6–8mm, with recurrences 10–12mm. Excisions were performed by dermatologists, with an incomplete excision rate of 18% in 1° tumours and 32% in recurrent tumours. Incomplete excisions were more likely in aggressive tumours and those around the eyes and ears; most were re-excised. The study showed no significant difference in recurrence rates at a mean of 2y. (See Table 29.3.)

Problems

- The incomplete excision rate seemed very high.
- Followed an ITT protocol, so even though four patients were randomized to excision and had their results counted in that group, they had MMS.
- The study's conclusion (that MMS be used for tumours bigger than 1cm in diameter and recurrent tumours) is not consistent with the results presented.
- Unclear if costs represented each procedure or the total cost per patient to treat initial disease, including treatment of incomplete excision.
- The BCCs undergoing MMS were curetted initially, but those in the surgical excision group were not.

Hypertrophic burn scars

Hypertrophic burn scars: analysis of variables.

AUTHORS: Deitch E, Wheelahan T, Rose M et al.

REFERENCE: *J Trauma* (1983) 10, 895–8.

STUDY DESIGN: Prospective, cohort.

EVIDENCE LEVEL: 3.

Key message

Burn healing period correlates with the risk of hypertrophic scarring. If the burn takes 14–21d to heal, there is a 33% risk of hypertrophic scarring. A healing period greater than 10d in Afro-Caribbean patients is associated with a higher risk of hypertrophic scarring.

Impact

This evidence gave additional impetus to the push for early excision/debridement of burns. Burns assessed to take longer than 14d to heal should be excised. Those of uncertain potential can be observed, and, if they remain unhealed at 10–14d, they should then be excised and grafted. Burns that are treated conservatively and take longer than 10–14d to heal should be treated with prophylactic compression garments.

Aims

Hypertrophic scarring is a major complication in patients experiencing thermal injury. This study aimed to determine the factors associated with an increased risk of development of hypertrophic burn scars.

Methods

Patients: 100 patients (245 burns) at one centre in the USA.

Inclusion criteria:

- Burns (superficial or moderate partial thickness) judged likely to heal within 3wk;
- Deeper burns in patients who refuse surgery.

Primary endpoint: Hypertrophic scars (increased thickness/elevation >2cm in diameter).

Secondary endpoint: Wound problems.

Follow-up: 9–24mo; assessed for hypertrophic scars.

Results

Baseline: 59 children, mean age 3y, total burn surface area (TBSA) average 14%; and 41 adults, mean age 37y, TBSA average 21%.

Wound problems:

- 38% of patients developed wound problems;
- 26% (63 of 245 wound sites) became elevated or hypertrophic.

Risk of hypertrophic scarring:

- 78% if the burn took longer than 21d to heal;
- 33% if healing occurred in 14–21d;
- If healing occurred in a shorter period than 14d, the risk of hypertrophic scar was markedly lower, except in Afro-Caribbean patients in whom the overall incidence of wound problems was 2× that of other populations. In this group, healing had to occur within 10d to reduce the risk of hypertrophic scar formation.

Discussion

This study showed the strong correlation between time to heal a burn and the formation of hypertrophic scars. It also showed the racial differences in hypertrophic scar formation. Furthermore, there was a difference in site, with the chest, upper limb, and foot found to be sites most likely to develop hypertrophic scarring. Compression or pressure garment use made no difference to the development of wound problems.

Problems

- This was an observational study, though it is unlikely that a prospective RCT could be performed, given the non-uniform mechanism of injury and the lack of equipoise, among other reasons. There was no statistical analysis of the significance of the results.
- The F/U period could have probably been longer, though, by 9mo, the tendency to hypertrophy would already be present.
- The inference that a less hypertrophic scar would result by surgically healing a burn that would take longer to heal, if treated conservatively, remains unproven.

Vacuum-assisted closure

Comparing conventional gauze therapy to vacuum-assisted closure wound therapy.

AUTHORS: Mouës C, van den Bemd G, Heule F et al.

REFERENCE: *J Plast Reconstr Aesthet Surg* (2007) **60**, 672–81.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First randomized trial to show vacuum-assisted closure (VAC) to be at least as good as gauze dressings.

Impact

Although the evidence base is limited, VAC is used by some as the panacea to all wounds. This study showed that, in carefully selected patients, VAC decreased contracture, compared to gauze-dressed wounds.

Aims

In patients requiring reconstructive surgery, wounds are often large, with extensive soft tissue loss. In many cases, immediate closure is not possible, with the first stage of management involving optimization of the wound condition through aggressive debridement in order to remove necrotic tissue, bacteria, and foreign material. This is conventionally followed by application of topical dressings. Drainage of wounds is important, with suction drainage combined with foam dressings having been an established surgical practice. VAC had recently been proposed as demonstrating efficacy in promoting wound healing. This study aimed to compare the use of VAC with gauze dressings in the treatment of acute (early-treated) and chronic (late-treated) surgically debrided full-thickness wounds awaiting surgical closure.

Methods

Patients: 54 wounds (29 vacuum and 25 gauze) at one centre in The Netherlands.

Inclusion criteria:

- Full-thickness wounds unable to be closed immediately due to crush, chronicity, or infection;
- Initial aggressive surgical debridement.

Exclusion criteria:

- Malignant disease;
- Exposed vessels, bleeding, or deep fistulae;
- Necrotic tissue or unstable skin around the wound;
- Osteomyelitis, uncontrolled diabetes, or psychiatric disorders.

Groups: Classified by early-treated wounds (≤ 4 wk) vs late-treated wounds (> 4 wk):

- Vacuum ($n = 29$; 12 early-treated, 17 late-treated);
- Conventional wet gauze dressings ($n = 25$; 8 early-treated, 17 late-treated).

Primary endpoint: Period until wound ‘ready’ for surgery (i.e. healthy granulations and good wound scores).

Secondary endpoints:

- Wound scores: inflammation, slough, exudates;
- Wound surface area;
- Bacterial count;
- Complications.

Follow-up: All wound measurements taken at the point when the wounds were considered ready for surgical closure. Bacterial count biopsies were performed every 2–3d. Wound scores at every dressing change (every 12h gauze and 48h vacuum).

Results

Table 29.4 Summary of results

| Primary endpoint | Vacuum | Gauze | <i>p</i> |
|-------------------------------|---------------------------|---------------------------|----------|
| Period to wound readiness | 6d | 7d | ns |
| Secondary endpoints | | | |
| Wound scores = ‘good’ | 69% in 1wk; 86% in 2wk | 56% in 1wk; 84% in 2wk | ns |
| Wound area reduction | 100% patients | 77% patients | <0.05 |
| Bacterial count | No change | No change | ns |
| Complications (preop) | 4/29 | 2/25 | ns |
| Treatment terminated | 2 (sepsis, necrosis) | 0 | ns |
| Large complications (post-op) | 4/25 | 3/21 | ns |
| Osteomyelitis | 4/29 | 1/25 | ns |

Discussion

The authors felt that VAC showed greatest difference in the ‘late’ group, though this was not statistically significant. Statistically, the significant differences were seen in the degree of wound contracture (with both techniques, but greater with VAC) and the daily relative wound score (significantly lower with VAC on d 3, 6, and 8 ($p < 0.05$), but not significant overall). Despite this, the trial concluded that vacuum therapy resulted in improved wound healing, compared with gauze therapy. (See Table 29.4.)

Problems

- The manufacturers of VAC supported the trial; unclear impact.
- Despite randomization by closed envelope assignment, unequal sample sizes occurred. Distribution of early and late wound types and mechanisms was unequal. Not all treatments were the same (e.g. 44% of the conventional group received topical antibacterial, whereas no patients in the vacuum group did).

Breast augmentation: type of implant

Textured or smooth implants for breast augmentation?

AUTHORS: Coleman D, Foo I, Sharpe D.

REFERENCE: *Br J Plast Surg* (1997) 50, 99–105.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Textured implants lead to greatly reduced capsular contracture, compared with smooth implants.

Impact

Textured implants have become the silicon breast implant shell of choice.

Aims

The incidence of adverse capsular contracture following breast augmentation is high (~30%), and many implant modifications have occurred to reduce this rate. Previous studies had largely been retrospective, leading to incomplete F/U and unequal comparison of implants. This trial was designed to compare textured silicon implants with smooth implants, to ascertain whether there was a difference in adverse capsular contracture rates.

Methods

Patients: 53 consecutive women (100 breasts) at one centre in the UK.

Inclusion criteria:

- 1° bilateral breast augmentation;
- Already on the waiting list for surgery.

Groups: Randomized in theatre after pocket dissection and sizing to:

- Smooth implant ($n = 48$ breasts);
- Textured implant ($n = 52$ breasts);

Textured or smooth implants were otherwise identical in shape and bleed characteristics, and were from the same manufacturer. All patients received intraoperative antibiotics, and the pocket was washed with 5% povidine iodine.

Primary endpoint: Baker grade of capsular contracture. Grade 1–2 = if patient said they could not feel the implant (i.e. normal appearance). Grade 3 = firm breast and abnormal appearance. Grade 4 = hard, painful breast with abnormal appearance.

Follow-up: At 1y, with questionnaires and clinical examination by one or more surgeons.

Results

Table 29.5 Summary of results

| Implant | Baker 1 and 2 (without contracture) | Baker 3 and 4 (with contracture) | Total (n) |
|----------|--|-------------------------------------|-----------|
| Smooth | 20 | 28 | 48 |
| Textured | 48 | 4 | 52 |
| Total | 68 | 32 | 100 |

$\chi^2 = 27.14$; $p < 0.0001$.

Discussion

This prospective RCT suggested that textured implants had markedly lower adverse capsular contraction rates. The reason for this is unknown. Subsequent studies have confirmed this finding, leading to textured implants becoming the shell of choice for bilateral augmentation. (See Table 29.5.)

Problems

- The only criterion used for capsular contracture was Baker's scale. This scale is a peculiar mixture of symptoms and signs, and is not objective.
- Not all patients were assessed by all three surgeons. Only one surgeon assessed some patients, although inter-rater reliability was rated as high.
- This trial confirmed benefit in using textured implants in both breasts. Subsequent studies have confirmed benefits in patients randomized to receive textured or smooth implants in either breast.

Breast reduction: drainage

Routine drainage is not required in reduction mammoplasty.

AUTHORS: Wyre S, Banducci D, Mackay D et al.

REFERENCE: *Plast Reconstr Surg* (2003) 111, 113–17.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First randomized trial to show that drains are unnecessary in routine breast reduction surgery.

Impact

This trial inspired a larger ($n = 150$) UK study that confirmed the findings. However, most surgeons still persist in draining breast reductions.

Aims

The use of closed suction drainage in reduction mammoplasty is standard practice in many centres; however, this is not evidence-based. Although it is believed that drainage reduces fluid accumulation, consequently leading to improved healing and cosmetic outcome, drainage itself is not without complication; in particular, drains cause discomfort to the patient, with some sources claiming that they can potentially increase post-operative infection rates. This study sought to clarify the situation.

Methods

Patients: 49 consecutive women at one centre in the USA.

Inclusion criteria: Routine breast reduction candidates:

- Bilateral breast reduction by the inferior pedicle technique.

Groups: Self-controlled—one breast each randomized to be:

- Drained;
- Undrained.

Primary endpoint: Complications (especially haematoma).

Secondary endpoints:

- Patient satisfaction (post-operative questionnaire to determine comfort level and overall satisfaction);
- Surgeon's aesthetic outcome assessment.

Follow-up: Drains removed on post-operative d 1. Average F/U 9mo (range 5–17mo).

Results

- Secondary endpoints: 17 of 19 patients reported that the undrained breast was more comfortable; two of 19 reported little/no difference between either breast;

Table 29.6 Summary of results

| Primary endpoint | Drained (n = 49) | Undrained (n = 49) | p |
|------------------|------------------|--------------------|----|
| Complications | 6 (12%) | 5 (10%) | ns |
| Haematoma | 1 (2%) | 1 (2%) | ns |

- Mean weight reduction: Drained breast = 675g (360–1,090g); undrained breast = 620g (380–1,011g);
- Surgeons' subjective observations: Undrained breast observed to be slightly more swollen and weepy (serous fluid) from suture line in first 24h. Differences were not appreciable after 48h. (See Table 29.6.)

Discussion

Routine drainage is commonplace, despite studies suggesting that reduction mammoplasty can be conducted safely, without the need for post-operative suction drainage. To date, there had never been a prospective study to address this issue. Although small, this trial was the first such prospective RCT to demonstrate that breast reductions could be safely left undrained, with comparable outcomes between groups. The patients served as their own controls, and the volumes excised were similar between drained and undrained breasts.

Problems

- Small numbers. F/U intervals were not recorded, and only 63% of patient questionnaires were returned.
- Randomization details were missing; it is unclear whether randomization was performed at the end of the operation (after all haemostasis had been completed) or at the beginning (allowing some bias to occur in the technique).
- Average excision volumes were smaller than in other studies on reduction mammoplasty. Furthermore, as the authors reported, there were no reductions >1,100g, hence, the applicability of these findings to large volume reductions is not possible.
- All but one patient underwent reduction using the inferior pedicle technique; correspondingly, the results are also not directly applicable to other reduction techniques.
- Different centres remove drains on different post-operative days; the authors of this study removed drains on the first post-operative day; hence, the effect of longer drainage was not observed.

Flexor tendon rehabilitation

Digital function following flexor tendon repair in Zone II: A comparison of immobilization and controlled passive motion techniques.

AUTHORS: Strickland J, Glogovac S.

REFERENCE: *J Hand Surg Am* (1980) 5, 537–43.

STUDY DESIGN: Controlled trial.

EVIDENCE LEVEL: 2a.

Key message

This is the first comparative study of rehabilitation techniques in flexor tendon repairs. It demonstrates the value of early mobilization.

Impact

Along with the non-comparative reports on the topic, this study changed the treatment of flexor tendon injuries to one of 1° repair and immediate mobilization.

Aims

Flexor tendon injuries in zone II (flexor tendon lacerations that lie within the flexor synovial sheath from the A1 pulley in the palm to the level of the insertion of the flexor digitorum superficialis (FDS) tendon on the middle phalanx) were considered as lying within 'no man's land', and surgeons were advised not to attempt 1° repair in this zone, due to complications of failure and stiffness. With a delayed approach being advocated (even though this required FDS excision, a tendon graft, and only average results after prolonged therapy), it was not until the first reports of Verdan (*J Bone Joint Surg* (1960) 42, 647–57) and others that successful 1° repair was demonstrated. These studies encouraged 1° repair in acute injuries but used immobilization as the rehabilitation protocol. Despite improved results over delayed repair, further improvements were sought; Kleinert subsequently published his technique of 'passive dynamic mobilization' (*J Hand Surg Am* (1977) 2, 441–51), involving rehabilitation with passive flexion and active extension, following tendon repair. This study aimed to compare the outcomes of immobilization, with the early use of the Duran and Houser (1975, Mosby) technique of passive mobilization (passive flexion and passive extension).

Methods

Patients: 37 patients with 50 consecutive flexor tendon injuries at one centre in the USA.

Inclusion criteria:

- Zone II flexor tendon injuries;
- Isolated injuries ± digital nerve injury.

Groups: Consecutively recruited:

- Immobilization for 3.5wk, then gradual motion ($n = 3$ had flexor digitorum profundus (FDP) tendon alone severed; $n = 22$ had FDP and FDS severed);
- Mobilization immediately with passive flexion, commencing active flexion at wk 4.5 with rubber band ($n = 8$ had FDP tendon alone severed; $n = 17$ had FDP and FDS severed).

Primary endpoint: Range of motion of interphalangeal joints—‘extensor lag’.

Secondary endpoint: Tendon rupture.

Table 29.7 Summary of results

| Primary endpoint | Immobilization | Mobilization | <i>p</i> |
|---------------------------|--|---|---|
| Range of motion | 0% excellent, 12% good, 28% fair, 11% poor | 36% excellent, 20% good, 16% fair, 24% poor | <0.005 [*] and <0.05 ^{**} |
| Secondary endpoint | | | |
| Rupture | 4 | 1 | Not stated |

^{*} For ‘excellent’ and ‘good’ groups; ^{**} for ‘excellent’, ‘good’, and ‘fair’ groups.

Follow-up: Average F/U 13mo.

Results

Discussion

Verdan first reported that 1° repair of flexor tendons in ‘no man’s land’ was a valid operation in fresh, cleanly cut wounds, which gave equal or better results than tendon grafts. However, he utilized a period of immobilization following repair. This study demonstrated an advantage, in terms of range of motion and rupture rate, when mobilization, rather than immobilization, was used as the rehabilitation method, following 1° flexor tendon repair. (See Table 29.7.)

Problems

- Patients were not randomized.
- Increasing surgeon experience with 1° tendon repair and rehabilitation may have biased the results.

Transplantation

Introduction 816

Kidney transplantation: preservation 818

Kidney transplantation: belatacept immunosuppression 820

Kidney transplantation: maintenance immunosuppression 822

Kidney transplantation: induction immunosuppression 824

Kidney transplantation: skin cancer 826

Kidney transplantation: desensitization 828

Kidney transplantation: deceased donors 830

Lung transplantation: preservation 832

Liver transplantation: immunosuppression 834

Cytomegalovirus infection: antivirals 836

Introduction

Organ transplantation is now a well-established therapy for selected patients with end-stage organ failure, for whom it is a lifesaving or life-enhancing experience. In the UK alone, over 3,000 organ transplants are carried out each year, and this figure would be much higher, were it not for the severe shortage of available organs. The majority of those fortunate enough to receive an organ transplant can now expect a good outcome, with average graft survival rates for kidney, liver, and heart transplantation in excess of 75% at 5y. Because transplantation is now regarded as an almost routine event in modern medical practice, it is easy to lose sight of how, not so long ago and certainly within the professional careers of the authors of this chapter, organ transplantation was a very hazardous procedure with a high chance of failure.

The first successful human kidney transplant was carried out between genetically identical twins in 1954 at the Peter Bent Brigham Hospital in Boston. This was a major advance but had little immediate impact on patient care, since the number of patients with kidney failure fortunate enough to have a healthy identical twin who wanted to give them a kidney was extremely small. Then, when the antiproliferative drug azathioprine was developed in the late 1960s and used together with steroids to prevent graft rejection, successful transplantation of kidney allografts from cadaveric donors became possible and was performed increasingly during the 1970s. The world's first successful liver transplant was performed by Tom Starzl at the University of Colorado in 1967, and the first heart transplant was carried out in the same year by Christiaan Barnard at the Groot Schuur Hospital in Cape Town, although the scientific foundations for heart transplantation had already been established by Norman Shumway in the USA. In these early days, randomized clinical trials were not needed to establish the benefits of organ replacement surgery, since the alternative was either certain death or lifelong dialysis.

The modern era of organ transplantation only really became firmly established in the 1980s, with the introduction of powerful new immunosuppressive agents, notably ciclosporin and subsequently tacrolimus. These new agents not only improved the results of renal transplantation, but also allowed the widespread development of liver and thoracic organ transplantation, which, prior to this, had been limited to very few centres worldwide. Along too came the first of many large multicentre clinical trials to determine how best to immunosuppress patients undergoing organ transplantation—a question still very much under investigation today.

Over the last 20y, the results of transplantation have improved incrementally for a variety of reasons, including better recipient selection, improved anaesthetic and surgical techniques, the introduction of more effective antiviral agents, and better post-transplant immunosuppressive management. Although new immunosuppressive agents have become available, ciclosporin and tacrolimus still remain the mainstay of most immunosuppressive regimens, despite their SEs, which ironically include nephrotoxicity. The problem of early graft loss from acute rejection is now uncommon,

and the main challenges today are chronic allograft rejection and the SEs of non-specific suppression of the immune response, namely infection and malignancy. Randomized clinical trials continue to inform and further improve clinical practice. Because transplantation today is such a success story, however, the traditional endpoints of 1y patient and graft survival are no longer sufficient, and new and more sophisticated endpoints are needed that reflect graft function and QoL after transplantation.

Kidney transplantation: preservation

Machine perfusion or cold storage in deceased-donor kidney transplantation.

AUTHORS: Moers C, Smits J, Maathuis MJ *et al.*

REFERENCE: *N Engl J Med* (2009) **360**, 7–19.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1a.

Key message

This is the largest RCT of machine perfusion and shows a benefit over cold storage, in terms of the need for dialysis in the first week post-transplant and improved graft survival.

Impact

Machine perfusion is being increasingly used but is still not routine, even in the regions of Europe in which the study was conducted.

Aims

Kidneys are flushed in the donor with cold preservation solution and then stored in the solution for transport to the recipient centre. Simple cold storage in an icebox is cheap and easy, but machine perfusion may offer a benefit by providing a continued flow of preservation fluid, stopping the accumulation of lactic acid and providing some nutrients to the stored kidney. The study aimed to determine whether machine perfusion resulted in more immediate function and better graft survival.

Methods

Patients: 662 recipients of kidneys from 336 deceased donors across Belgium, The Netherlands, and Northern Germany.

Inclusion criteria:

- Donor age ≥ 16 y;
- Brain dead (donation after brain death, DBD) or controlled circulatory death (donation after circulatory death, DCD) donors.

Both kidneys were transplanted into two different recipients.

Exclusion criteria:

- One recipient died within the first week (i.e. did not reach primary endpoint);
- One kidney used as part of a multiorgan transplant.

Groups:

- Static cold storage (CS) in either University of Wisconsin (UW) static cold storage solution or histidine–tryptophan–ketoglutarate (HTK);
- Machine perfusion (MP) with UW MP solution using an Organ Recovery Systems LifePort kidney transporter. Pulsatile flow, fixed pressure of 30mmHg; 1–8°C.

Perfusion was performed by a team of trained perfusionists. Kidneys were randomized to either MP or CS, but random allocation could be switched if the kidney had multiple arteries or a small aortic patch and so could not be placed on the machine.

Primary endpoint: Delayed graft function (DGF) (need for dialysis in the first post-transplant week).

Secondary endpoints: Duration of DGF; 1° non-function (permanent lack of function); acute rejection; graft and patient survival.

The study was powered to detect a 10% reduction in DGF from 35% with an 80% power if 300 pairs were recruited. Analysis by treatment.

Follow-up: At 12mo.

Results

- A total of 654 potential donors, 359 randomized, 336 included in the study. Exclusions included seven technical failures of MP, 14 kidneys rejected by the transplant centre. (See Table 30.1.)

Table 30.1 Summary of results

| Primary endpoint | MP (n = 336) | CS (n = 336) | Significance |
|-------------------------------------|--------------|--------------|--------------|
| DGF | 70 (20.8%) | 89 (26.5%) | 0.05 |
| Secondary endpoints | | | |
| Functional DGF* | 77 (22.9%) | 101 (30.1%) | 0.03 |
| 1° non-function | 7 (2.1%) | 16 (4.8%) | ns |
| Duration of DGF Median days (range) | 10 (1–48) | 13 (1–41) | 0.04 |
| Graft survival at 12mo* | 94% | 90% | 0.04 |
| Patient survival | 97% | 97% | ns |

* Absence of a decrease in serum creatinine of at least 10% per day for 3 consecutive days.

Discussion

This study showed that machine perfusion reduced the incidence of DGF, compared to static cold storage. Graft survival was also better, particularly in the older donors, but the study was not powered sufficiently for this endpoint. Subsequent analysis of subgroups showed that extended criteria donors (age over 60 or over 50, and two of HTN, raised creatinine, and death from CVA) benefit, in terms of graft survival and DGF, but DCD donors only show a benefit in reduction in DGF, and not graft survival.

Problems

- The CS arm did not receive a standard treatment.
- The study was not powered to show differences in graft survival.

Kidney transplantation: belatacept immunosuppression

A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study)

AUTHORS: Vincenti F, Charpentier B, Vanrenterghem Y *et al.*

REFERENCE: *Am J Transplant* (2010) **10**, 535–46.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Belatacept maintenance immunosuppression is associated with superior renal function at 1y, compared to ciclosporin-treated patients.

Impact

The superior renal function should make belatacept an attractive agent, but its uptake has been hampered by its high cost, relative to other maintenance agents such as tacrolimus.

Aims

Belatacept stops T-lymphocyte activation by blocking co-stimulation via the CD28 pathway. This study aimed to determine whether immunosuppression with belatacept would provide superior renal function and similar rates of acute rejection at 12mo, compared to ciclosporin.

Methods

Patients: 686 adult kidney transplant recipients at 21 European and American centres were randomized to one of three regimens.

Inclusion criteria:

- Standard criteria donors (excluding DCD and extended criteria donors);
- Anticipated cold ischaemic time <24h;
- Not sensitized to human leucocyte antigens (HLAs) (first transplant recipients with panel-reactive antibody <50% or re-transplant <30%).

Groups:

- A: Belatacept moderate intensity (MI) ($n = 225$);
- B: Belatacept low intensity (LI) ($n = 230$);
- C: Ciclosporin ($n = 231$).

All groups received basiliximab on d 0 (day of transplant) and d 4, together with MMF 2g/d PO and corticosteroids. Belatacept (10mg/kg) was given IV on d 1 and 5, and wk 2, 4, 8, and 12, and then 5mg/kg every 4wk from mo 3 to 12 in the LI group; the MI group received 10mg/kg on d 1 and 5, and wk 2, 4, 6, 8, 10, 12, 16, 20, and 24, and then 5mg/kg every 4wk to 12mo.

Primary endpoints (three co-primary endpoints):

- Patient and graft survival;
- Renal impairment: % of patients with GFR $<60\text{mL/min/m}^2$ at 12 mo or decrease in GFR $\geq 10\text{mL/min/1.73m}^2$ from mo 3 to 12;
- Biopsy proven rejection;

Secondary endpoints:

- GFR (measured using iothalamate and estimated by MDRD formula);
- Biopsy-proven prevalence of chronic allograft nephropathy on 12mo protocol biopsy;
- Metabolic: Incidence of new-onset diabetes (NODAT);
- CV: BP.

Follow-up: Up to 12mo.

Results

Table 30.2 Summary of results

| Primary endpoint* | MI (n = 219) | LI (n = 226) | CyA (n = 221) |
|--|--------------|--------------|---------------|
| Surviving with functioning kidney | 209 (95%) | 218 (97%) | 206 (93%) |
| Renal impairment | 115 (55%) | 116 (54%) | 166 (78%) |
| Acute rejection | 49 (22%) | 39 (17%) | 16 (7%) |
| Secondary endpoints | | | |
| Incidence of NODAT at 12mo | 11 (7%) | 7 (4%) | 16 (10%) |
| Non-HDL cholesterol: mean change from baseline, mg/dL (SE) | 8.1 (2.8) | 8.0 (2.8%) | 18.3 (2.8) |
| Triglycerides: mean change from baseline, mg/dL (SE) | -17.0 (7.0) | -21.2 (6.9) | 6.6 (6.9) |
| SBP: mmHg (SD) | 133 (16.2) | 131 (16.5) | 139 (20.1) |
| DBP: mmHg (SD) | 79 (11.6) | 79 (10.9) | 82 (11.2) |

* For primary endpoint: no difference in MI or LI and CyA for patient and graft survival at 1y; renal function was superior in MI and LI groups, compared to CyA, with better measured and calculated GFR.

Discussion

Belatacept was associated with less renal impairment and a mean measured GFR at least 13mL/min/1.73m^2 better than ciclosporin-treated patients at 12mo. It was also associated with a better metabolic and CV profile than the ciclosporin-based regimen. These findings were similar to the BENEFIT-EXT study, a similar study conducted with extended criteria and DCD donor kidney transplants. In both studies, there was a worrying small excess of post-transplant lymphoproliferative disorder in EB-virus naïve recipients. (See Table 30.2.)

Problems

- Ciclosporin comparator arm is not standard therapy.
- Incidence of acute rejection is much higher in belatacept groups.

Kidney transplantation: maintenance immunosuppression

ELITE (Efficacy Limiting Toxicity Elimination) **Symphony**: Reduced exposure to calcineurin inhibitors in renal transplantation.

AUTHORS: Ekberg H, Tedesco-Silva H, Demirbas A *et al.*

REFERENCE: *N Engl J Med* (2007) 357, 2562–75.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Low-dose tacrolimus, combined with MMF and corticosteroids, is associated with better renal function and a lower incidence of acute rejection.

Impact

The largest investigator-led study in transplantation, it is generally believed to have defined the best immunosuppressive protocol for kidney transplantation and the benchmark against which others should be compared.

Aims

Calcineurin inhibitors (CNIs) have been the mainstay of immunosuppression in kidney transplantation since the 1980s, but the best regimen is uncertain, in particular to minimize CNI nephrotoxicity. The availability of sirolimus also poses a question regarding its role in maintenance immunosuppression. This study was constructed in order to address these questions.

Methods

Patients: 1,645 adult kidney transplant recipients at 83 sites in 15 countries.

Inclusion criteria:

- First or second live or deceased donor kidney transplant alone;
- Not highly sensitized to HLA antigens (<80% panel-reactive antibodies, PRAs).

Exclusion criteria:

- Need for treatment with a non-study immunosuppressant, MTX, or cyclophosphamide;
- Sensitized to HLA antigens (PRA >20%);
- Cold ischaemic time ≥ 30 h;
- Previous CD25 monoclonal antibody therapy.

Groups:

- A: Standard-dose ciclosporin ($n = 390$)—target level 150–300ng/mL for 3mo, then 100–200ng/mL thereafter;
- B: Low-dose ciclosporin ($n = 399$)—target level 50–100ng/mL throughout;
- C: Low-dose tacrolimus ($n = 401$)—target level 3–7ng/mL throughout;
- D: Low-dose sirolimus ($n = 399$)—target level 4–8ng/mL throughout.

All groups received corticosteroids and MMF; groups B, C, and D received daclizumab CD25 monoclonal antibody induction therapy.

Primary endpoint: Estimated GFR at 12mo (Cockcroft–Gault).

Secondary endpoints:

- Measured GFR at 12mo (24h urine collection);
- Incidence of acute rejection;
- Treatment failure in first 12mo;
- Patient and graft survival;
- Incidence of DGF.

Follow-up: Up to 12mo.

Results

- A total of 1,589 eligible patients, on an ITT basis;
- 12mo data (see Table 30.3).

Table 30.3 Summary of results

| Primary endpoint | Full cyclo | Low cyclo | Low tacrol | Low sirol | p |
|-------------------------------|---------------|--------------|---------------|--------------|--------|
| Calculated GFR (mL/min) | 57.1 | 59.4 | 65.4 | 56.7 | <0.001 |
| Secondary endpoints | | | | | |
| Measured GFR (mL/min) | 63.5 | 65.3 | 69.6 | 64.4 | 0.04 |
| Biopsy-proven acute rejection | 30.1% | 27.2% | 15.4% | 40.2% | <0.001 |
| Graft survival* | 91.9% | 94.3% | 96.4% | 91.7% | 0.02 |
| Patient survival | 96.5% | 98.2% | 97.2% | 96.8% | ns |
| Treatment failure | 22.8% | 20.1% | 12.2% | 35.8% | <0.001 |
| DGF | 33.6% | 32.4% | 35.7% | 21.1% | 0.004 |

* Censored for death with a functioning graft.

Discussion

This study demonstrated that the low-dose tacrolimus regimen was superior, in terms both of optimizing renal function and minimizing acute rejection.

Problems

- The actual mean tacrolimus level was around 7ng/mL, so the low-dose tacrolimus group was *not* low-dose.
- The low-dose ciclosporin group dose level was also higher than the target, with a maintenance phase level of around 100ng/mL.
- The results for sirolimus are at odds with other smaller studies in which higher doses were used.

Kidney transplantation: induction immunosuppression

INTAC (Induction with **T**acrolimus study): Alemtuzumab induction in renal transplantation.

AUTHORS: Hanaway MJ, Woodle ES, Mulgaonkar S *et al.*

REFERENCE: *N Engl J Med* (2011) **364**, 1909–19.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

As one of the largest RCTs of alemtuzumab in kidney transplantation, this showed less acute rejection in low-risk patients. Antithymocyte globulin (ATG) and alemtuzumab had similar efficacy in high-risk patients. All patients could be managed with early steroid withdrawal.

Impact

The use of alemtuzumab and ATG remains high, although recent withdrawal of alemtuzumab, pending rebranding with a licence for MS, places its future in doubt.

Aims

Conventional induction therapy for kidney transplantation in the UK is basiliximab, while, in the USA, rabbit (r) ATG is also commonly used. Alemtuzumab, a lymphocyte-depleting antibody originally licensed in leukaemia, has increasingly been used. This trial aimed to evaluate the role of alemtuzumab induction in patients at low risk (normal immunological risk) and high risk (believed more likely to experience rejection). All patients underwent early steroid withdrawal.

Methods

Patients: 139 high-risk patients and 335 low-risk patients in the USA.

Inclusion criteria:

- Adults ≥ 18 y;
- At least one HLA class I or II mismatch.

Exclusion criteria:

- Expanded criteria kidneys or kidneys DCD;
- Positive flow or cytotoxic cross-match;
- Ischaemic time over 36h.

Groups:

- Low-risk: first transplant, PRA $< 20\%$, not black race ($n = 335$);
 - Basiliximab, 20mg on d 0 and either d 3, 4, or 5 ($n = 171$);
 - Alemtuzumab ($n = 164$);
- High-risk: repeat transplant; peak or current HLA (PRA level $\geq 20\%$; black race) ($n = 139$);
 - rATG 1.5mg/kg on d 0, 1, and 2, and d 3 or 4 ($n = 69$);
 - Alemtuzumab 30mg at induction ($n = 70$).

All received: tacrolimus, MMF, and 5d of steroids.

Primary endpoint: Acute rejection episodes at 6 and 12mo.

Secondary endpoints:

- Patient and graft survival;
- Kidney function;
- Incidence of cancer and infection.

Follow-up: Up to 36mo.

Results

Table 30.4 Summary of results

| | Low-risk | | p | High-risk | | p |
|--|----------|----------|--------|-----------|----------|----|
| | Basil | Alem | | p | rATG | |
| Primary endpoint | | | | | | |
| Acute rejection during first 6mo | 18% | 2% | <0.001 | 9% | 6% | ns |
| Acute rejection during first 12mo | 20% | 3% | <0.001 | 13% | 10% | ns |
| Secondary endpoints | | | | | | |
| Graft survival at 3y | 92% | 93% | ns | 84% | 91% | ns |
| Patient survival at 3y | 92% | 93% | ns | 91% | 99% | ns |
| Serious adverse events | | | | | | |
| CV | 17 (10%) | 15 (9%) | ns | 8 (12%) | 2 (3%) | ns |
| Infection | 38 (22%) | 57 (35%) | 0.02 | 23 (33%) | 19 (27%) | ns |
| Cancer | 3 (2%) | 7 (4%) | ns | 0 | 4 (6%) | ns |
| Graft survival not censored for death. | | | | | | |

Graft survival not censored for death.

Discussion

Alemtuzumab and rATG were equally efficacious in patients at higher risk of acute rejection, with less acute rejection than basiliximab-treated low-risk patients. However, alemtuzumab was associated with more infections and leucopenia than basiliximab. All patients were managed without maintenance corticosteroids. (See Table 30.4.)

Problems

- There was no comparison of renal function between the groups.
- Alemtuzumab has been associated with late autoimmune complications; this was not analysed in the study.
- Antibody-mediated rejection reportedly commoner with alemtuzumab. Data not formally collected in this study, but retrospective analysis suggests no excess.

Kidney transplantation: skin cancer

Sirolimus and secondary skin-cancer prevention in kidney transplantation.

AUTHORS: Euvrard S, Morelon E, Rostaing L et al.; TUMORAPA Study Group.

REFERENCE: *N Engl J Med* (2012) **367**, 329–39.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First randomized trial to show that switching from CINs to sirolimus maintenance immunosuppression prevents 2° skin cancer in renal transplant recipients.

Impact

Switching to sirolimus-based immunosuppression should be considered in patients who have had a squamous cell skin cancer, to reduce the risk of 2° cancers.

Aims

Immunosuppressive therapy in renal transplant recipients is associated with a high risk of squamous cell cancer of the skin, and those affected are likely to develop multiple further skin cancers. Immunosuppressive regimens are usually based on a CIN (ciclosporin or tacrolimus), but the mammalian target of rapamycin (mTOR) inhibitor sirolimus has both immunosuppressive and anti-neoplastic properties. This trial examined whether switching patients who had already developed a squamous cell cancer from CIN-based immunosuppression to sirolimus prevented the development of 2° skin cancer.

Methods

Patients: 120 patients (from a total of 129 randomized) at centres in Europe.

Inclusion criteria:

- Recipients of a first or subsequent renal transplant;
- Stable renal transplant function while on CIN-based immunosuppression;
- At least one previous squamous cell skin cancer (excluding carcinoma *in situ* lesions).

Exclusion criteria:

- Metastatic squamous cell skin cancer;
- Multiorgan transplantation.

Groups:

- Sirolimus ($n = 64$);
- CIN ($n = 56$).

Primary endpoint: Survival free from new cutaneous squamous cell carcinoma at 2y.

Secondary endpoints: Time until onset of new cutaneous squamous cell carcinoma, occurrence of other skin and non-skin tumours, graft function, and safety.

Follow-up: Review by dermatologist and nephrologist every 3mo until 2y.

Results

- New cutaneous squamous cell carcinomas developed in 22% of patients randomized to sirolimus and 39% of those randomized to CIN (RR 0.56; 95% CI 0.32–0.98) after a median time of 15mo and 7mo, respectively ($p = 0.02$);
- Serious adverse events (particularly pneumonitis) were commoner in the sirolimus group (average 0.94 vs 0.25/patient), and adverse events occurred more often in those who converted to sirolimus rapidly. Overall, 23% of patients discontinued sirolimus therapy, because of adverse events;
- There were no episodes of graft rejection in either group.

Discussion

There is abundant experimental and clinical evidence that mTOR inhibitors have anti-tumour effects, but this is the first randomized trial to confirm that their use protects kidney transplant recipients who have had a squamous cell cancer of the skin from developing further such cancers. Although many transplant patients tolerate switching to sirolimus poorly, especially if they are switched rapidly, early conversion should be considered in patients with cutaneous squamous cell carcinomas.

Problems

- The F/U period for the study was relatively short, and the protocol for switching to sirolimus was not standardized.
- The occurrence of new carcinomas was observed only quarterly, and so the precise time to recurrence was unknown.
- The mechanisms responsible for the beneficial effects of sirolimus in this study also remain uncertain, and a specific anti-neoplastic effect of sirolimus, rather than an effect related to the overall level of immunosuppression in the context of the study, remains speculative.

Kidney transplantation: desensitization

Desensitization in HLA-incompatible kidney recipients and survival.

AUTHORS: Montgomery R, Lonze B, King K *et al.*

REFERENCE: *N Engl J Med* (2011) **365**, 318–26.

STUDY DESIGN: Observational cohort study.

EVIDENCE LEVEL: 3.

Key message

In patients sensitized to HLA, live donor kidney transplantation after antibody removal provides a significant survival benefit over remaining on the transplant waiting list for a compatible deceased donor kidney.

Impact

Sensitized patients with an HLA-incompatible potential living kidney donor should be considered for desensitization therapy to allow living donor kidney transplantation to proceed safely, as an alternative to waiting for a compatible deceased donor kidney to become available.

Aims

Many patients waiting for a kidney transplant have antibodies to HLA antigens as a result of pregnancy, blood transfusion, or a failed previous transplant, and this limits their chance of being offered an HLA antibody-compatible deceased donor kidney. An alternative approach is to perform live donor kidney transplantation after depletion of donor-specific HLA antibodies. However, outcomes after desensitization in earlier studies were inferior to those reported for compatible live donor transplantation. This study sought to determine whether this provides a survival advantage over waiting for an HLA-compatible kidney.

Methods

Patients: 211 patients in the USA.

Inclusion criteria:

- Treatment group: Patients with end-stage chronic renal failure and an HLA antibody-incompatible living donor deemed suitable for desensitization and transplantation;
- Matched controls on the waiting list for deceased donor transplantation were identified retrospectively from the transplant registry.

Groups:

- Treatment group: Desensitization (plasmapheresis and low-dose IVIG) ($n = 211$);
- Matched control group: Dialysis or transplantation with an HLA antibody-compatible deceased donor kidney ($n = 1,040$);
- Matched control group: Dialysis only ($n = 1,050$).

Primary endpoint: Mortality after kidney transplantation.

Follow-up: 8y after kidney transplantation in the study group, and for a similar duration in the control groups.

Adverse events associated with desensitization were recorded in the study group.

Results

- A total of 98% of patients who started plasmapheresis progressed to live donor kidney transplantation. Patient survival in the group treated with desensitization was superior to that in both matched control groups ($p < 0.001$ for both comparisons). A total of 1.4% of patients had a major adverse event related to plasmapheresis, and 6.8% of desensitized patients required a return to the operating theatre after transplantation for bleeding from the surgical or renal biopsy site. (See Table 30.5.)

Table 30.5 Summary of results

| Group | Graft survival | | | |
|-----------------------------|----------------|------|-----|-----|
| | 1y | 3y | 5y | 8y |
| Desensitization | 91% | 86% | 81% | 81% |
| Dialysis or transplantation | 93% | 77% | 66% | 49% |
| Dialysis only | 91% | 67 % | 52% | 31% |

Discussion

This important study shows that, for patients with an HLA antibody-incompatible living donor, desensitization allows kidney transplantation with acceptable results, albeit not as good as those typically reported for living donor kidney transplantation with an HLA antibody-compatible donor. Desensitization represents an alternative approach to paired or pooled donation, in which another HLA antibody-incompatible living donor pair is identified through a two- or three-way exchange. Desensitization is not, however, a suitable approach for facilitating HLA antibody-incompatible deceased donor transplantation, because the availability of a deceased donor organ in a suitable time frame cannot usually be guaranteed.

Problems

- This is a single-centre study with retrospective comparator groups.
- Confounding factors in the comparison groups cannot be excluded.
- The length of F/U after transplantation is not very long in some desensitized patients.

Kidney transplantation: deceased donors

Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study.

AUTHORS: Summers D, Johnson R J, Hudson A *et al.*

REFERENCE: *Lancet* (2013) **381**, 727–34.

STUDY DESIGN: Observational cohort study.

EVIDENCE LEVEL: 3.

Key message

Kidneys from circulatory death donors (DCD donors) have equivalent graft survival to those from brain death donors (DBD donors). Increasing donor age is associated with similarly poorer outcome for DCD and DBD donor kidneys, but kidneys from DCD donors are less tolerant to long periods of cold storage prior to transplantation.

Impact

While increasing donor age is a risk factor for inferior outcome after transplantation, decisions about the use of kidneys from older DCD donors should be the same as those for kidneys from DBD donors. Because increased cold storage time for kidneys from DCD donors is associated with inferior outcomes, organ-sharing schemes need to balance the benefits of organ sharing against the risk of extending cold ischaemic times by organ transport.

Aims

In recent years, there has been a large increase in the number of kidneys donated from deceased donors where death has been certified after cessation of cardiopulmonary function following the withdrawal of life-supporting treatment. Kidneys from such donors incur a variable period of warm ischaemic injury in the period from between cessation of cardiopulmonary function and perfusion with cold organ preservation solution, but previously published UK registry data (*Lancet* (2010) **376**, 1303–11) suggest that the long-term outcome of kidneys from DBD and DCD donors is very similar. However, many potential DCD donors are aged >60y, and some clinicians remained reluctant to transplant kidneys from such donors, due to concerns about the likely outcome. This study aimed to establish the effect of donor age and duration of cold ischaemic time on DCD kidney transplant outcome.

Methods

Patients: 6,490 deceased donor kidney transplants undertaken in 23 UK centres.

Inclusion criteria:

- Recipients of deceased donor renal transplants from 1 January 2005 to 1 November 2010;
- Kidneys from donors of all ages.

Exclusion criteria:

- Recipients ≤ 18 y;
- Recipients of kidneys from uncontrolled DCD donors;
- Recipients of non-renal organ transplants.

Groups:

- Recipients of kidneys from DCD kidneys ($n = 1,768$);
- Recipients of kidneys from DBD donors ($n = 4,127$).

Primary endpoint: Graft survival at 3y.

Secondary endpoints: Patient survival, 1° non-function, DGF, and eGFR.

Follow-up: At least 3y

Results

- Graft survival at 3y was similar for recipients of DCD vs DBD donor kidneys (HR 1.14, 95% CI 0.95–1.36, $p = 0.16$). Recipients of kidneys from donors $>60y$ was inferior, irrespective of donor type (see below). Graft survival for recipients of DCD, but not DBD, kidneys with cold ischaemia of $>24h$ was inferior. (See Table 30.6.)

Table 30.6 Summary of results

| | HR (95% CI) | p for interaction | |
|---------------------|------------------|-------------------|-------|
| Donor age | | | |
| <40y | 1.0 | 1.0 | |
| 40–59y | 1.73 (1.20–2.49) | 1.60 (1.22–2.01) | 0.66 |
| ≥60y | 2.76 (1.87–4.08) | 2.16 (1.63–2.86) | 0.30 |
| Cold ischaemic time | | | |
| <12h | 1.0 | 1.0 | |
| ≥12 and <18h | 1.53 (1.03–2.30) | 0.99 (0.75–1.30) | 0.07 |
| ≥18 and <24h | 1.43 (0.92–2.22) | 1.03 (0.76–1.40) | 0.22 |
| ≥24h | 2.36 (1.39–4.02) | 0.94 (0.66–1.35) | 0.004 |

Discussion

This large and comprehensive analysis confirms another recent UK renal transplant registry analysis showing the outcome in recipients of kidneys from DCD donors is comparable to that for kidneys from DBD donors (*Lancet* (2010) **376**, 1303–11). This is the first study to show that, while increasing donor age is associated with inferior outcome, there is no difference between DCD and DBD kidneys from older donors. Decisions about whether to use kidneys from older DCD donors should therefore be based on the same criteria as for kidneys from DBD donors, which will lead to more widespread use of older DCD donor kidneys. However, kidneys from circulatory death donors tolerate cold storage less well, a factor to consider when planning organ allocation.

Problems

- As a registry analysis, confounding factors cannot be certainly excluded.
- The subgroup analysis was confined to first-time recipients.
- Limited F/U limits long-term graft outcome conclusions.

Lung transplantation: preservation

Normothermic ex vivo lung perfusion in clinical lung transplantation.

AUTHORS: Cypel M, Yeung J, Liu M et al.

REFERENCE: *N Engl J Med* (2011) **364**, 1431–40.

STUDY DESIGN: Prospective, non-randomized study.

EVIDENCE LEVEL: 2a.

Key message

Ex vivo lung perfusion (EVLP) allows identification of high-risk donor lungs, which will produce results equivalent to standard lungs following transplantation.

Impact

EVLP is being evaluated in a number of randomized trials and, if the results are positive, will transform lung transplantation by vastly increasing the supply of lungs.

Aims

Many potential donor lungs are deemed unsuitable for transplantation, due to acute lung injury (ALI) sustained during brain death or as a consequence of prolonged ventilation prior to death. Around 15% of lungs from multi-organ donors are used for transplantation; mortality on the waiting list is around 20%. This study examined the utility of EVLP to enable assessment of function prior to transplantation.

Methods

Patients: Lungs from 134 donors transplanted to 136 patients in Toronto between September 2008 and January 2010.

Inclusion criteria:

- Best $\text{PaO}_2:\text{FiO}_2$ ratio $<300\text{mmHg}$;
- Pulmonary oedema (bilateral infiltrates without evidence of infection);
- Poor lung deflation or inflation during intraoperative donor assessment;
- Donor blood transfusion over 10U;
- Donation after circulatory death.

Exclusion criteria:

- Gastric aspiration;
- Established pneumonia;
- Severe mechanical lung injury, e.g. contusions in multiple lobes.

Groups: Lungs were perfused ex vivo for 4h, using an acellular perfusate, with function assessed hourly.

- High-risk donor ($n = 23$);
- Standard-risk donor ($n = 111$).

Primary endpoint: 1° graft dysfunction, grade 2 ($\text{PaO}_2:\text{FiO}_2$ 200–300mmHg) or grade 3 ($\text{PaO}_2:\text{FiO}_2 <200\text{mmHg}$).

Secondary endpoints:

- Graft function on return to ICU following transplantation;
- Need for ECMO;
- Bronchial complications requiring intervention;
- Duration of mechanical ventilation;
- ICU stay;
- 30d mortality.

Follow-up: Minimum of 1y.

Results

- Lungs from three of the 23 donors had worsening function during EVLP and were not used; 20 were transplanted; 75% of high-risk lungs were transplanted as a double-lung transplant, 85% of control lungs.
- There was no difference in the incidence of 1° graft dysfunction on return to ICU, at 24 or 48h, or in the duration of mechanical ventilation; no EVLP patient required ECMO. (See Table 30.7.)

Table 30.7 Summary of results

| | EVLP (n = 20) | Standard (n = 116) | p |
|-----------------------------------|---------------|--------------------|----|
| 1° graft dysfunction at 72h | 15.0% | 30.1% | ns |
| Bronchial complications | 5% | 4% | ns |
| Mortality at 30d after transplant | 2 (10%) | 6 (5.2%) | ns |
| Survival at 1y | 16 (80%) | 97 (83.6%) | ns |

Discussion

This is a small, but significant, experience showing the use of EVLP to enable transplantation of lungs that would not normally be transplanted. Further evaluation is necessary, but EVLP has already resulted in a change of attitude among lung transplant surgeons, and this experience, together with that of its pioneers Stig Steen and colleagues in Sweden, has prompted systemic evaluation of the technique and an increase in lung usage.

Problems

- This was a small, non-randomized study demonstrating the feasibility of EVLP, but the technique needs more rigorous evaluation in a randomized manner.

Liver transplantation: immunosuppression

A randomized, multicenter study comparing steroid-free immunosuppression and standard immunosuppression for liver transplant recipients with chronic hepatitis C.

AUTHORS: Klintmalm G B, Davis G L, Teperman L et al.

REFERENCE: *Liver Transplantation* (2011) 17, 1394–403.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Largest RCT to show that, while steroid avoidance is safe and effective in terms of graft rejection, it does not reduce the incidence of HCV recurrence following liver transplantation.

Impact

Steroid-sparing regimens are safe and effective but cannot be promoted on the basis that they reduce HCV recurrence in patients with chronic HCV undergoing liver transplantation.

Aims

Recurrence of HCV is common in patients with chronic HCV undergoing liver transplantation and leads to worse long-term outcome. It has been suggested steroids may accelerate the development of aggressive recurrent HCV, prompting the use of steroid-sparing immunosuppressive regimens in such patients. This trial examined whether steroid-free maintenance immunosuppressive regimens were safe, effective, and beneficial, in terms of HCV recurrence, in patients undergoing liver transplantation.

Methods

Patients: 294 adults from 18 liver transplant centres in the USA.

Inclusion criteria:

- Recipients with end-stage liver disease due to HCV undergoing liver transplantation;
- Recipients of livers from deceased or living donors.

Exclusion criteria:

- Previous transplantation;
- Hospitalized in intensive care at time of transplantation;
- Hepatitis B surface antigen positive;
- Recipients of livers from donors with HCV antibodies.

Groups:

- Tacrolimus and corticosteroids ($n = 77$);
- Tacrolimus, corticosteroids, and MMF ($n = 77$);
- Daclizumab induction, tacrolimus, and MMF ($n = 146$).

Endpoints:

- Primary: Advanced recurrent HCV (grade 3 or higher) in first 2y;
- Acute cellular rejection confirmed by liver biopsy;
- Complications (including new-onset diabetes and HTN, infection, and malignancy);
- Withdrawal of immunosuppression or change to other regimen.

Follow-up: Protocol liver biopsy at 90d, and at 1 and 2y.

Results

Table 30.8 Summary of results

| Endpoint | Tac/steroids | Tac/steroids/ MMF | Tac/MMF/ dacliz | p |
|---|--------------|----------------------|--------------------|----|
| Severe HCV recurrence (2y) | 35.4% | 24.3% | 33.9% | ns |
| Patient survival (2y) | 83.8% | 81.0% | 86.1% | ns |
| Graft survival (2y) | 79.1% | 79.8% | 85.1% | ns |
| Acute cellular rejection (2y) | 14.3% | 12.5% | 13.7% | ns |
| Infection requiring IV antibiotics (1y) | 41.6% | 36.1% | 34.8% | ns |
| New-onset insulin-dependent diabetes (1y) | 29.8% | 32.8% | 18.6% | ns |
| New-onset HTN (1y) | 79.0% | 70.5% | 66.5% | ns |

- Steroid avoidance made no difference to HCV progression (primary endpoint) or other complications, although there was a trend towards reduced incidence of diabetes in the steroid-free group. (See Table 30.8.)

Discussion

Avoiding steroid use has several potential advantages in liver transplant recipients, and this study clearly showed that steroid avoidance was safe in recipients undergoing liver transplantation for HCV infection. Unfortunately, steroid avoidance did not reduce the impact of recurrent HCV infection, which remains a major cause of morbidity in this patient group.

Problems

- Patients were only followed up for 2y after transplantation, and some refused liver biopsy in the second year (up to 18%). This may have masked potential differences in HCV progression between groups.
- Although acute rejection rates were similar, rejection-driven changes to immunosuppression (e.g. steroid boluses) may have also masked differences between groups.
- The study was not powered to detect differences in complication rates.
- While the use of antiviral therapy to treat HCV appeared similar in the three groups, it was not part of the protocol, and so information on treatment dose, duration, and outcome was not available for analysis.

Cytomegalovirus infection: antivirals

VICTOR study: Oral valganciclovir is noninferior to intravenous ganciclovir for the treatment of cytomegalovirus disease in solid organ transplant recipients.

AUTHORS: Asberg A, Humar A, Rollag H *et al.* (Victor Study Group).

REFERENCE: *Am J Transplant* (2007) **7**, 2106–13.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This large, multicentre, randomized, open-label study provides the best evidence to date that oral valganciclovir is as safe and effective as IV ganciclovir for the treatment of non-life-threatening (mild to moderate) CMV infection (including tissue-invasive disease) in recipients of solid organ transplants.

Impact

All patients can be given oral valganciclovir, with the advantage that treatment can be continued on an outpatient basis, as it does not require IV administration.

Aims

Despite preventative strategies, CMV disease remains a major problem following solid organ transplantation, responsible for considerable morbidity. Although IV ganciclovir is usually an effective treatment, it requires long-term IV access and frequent hospital admission, which is expensive and inconvenient for patients. Oral valganciclovir has been proposed to provide a simpler and more convenient alternative. This open-label, active, drug-controlled, non-inferiority study aimed to determine whether oral valganciclovir (an oral prodrug of ganciclovir, providing improved bioavailability) was as safe and effective as IV ganciclovir for treating CMV infection.

Methods

Patients: 321 adult recipients of solid organ transplants at 42 international centres—74% renal, 7% liver, and 6% heart transplantation.

Inclusion criteria: Virological and clinical evidence of CMV disease.

Exclusion criteria: Life-threatening CMV disease (as defined by local investigators).

Groups:

- Valganciclovir (900mg bd) ($n = 164$);
- Ganciclovir (5mg/kg IV bd) ($n = 157$);
- Trial drugs were for 21d, and doses adjusted according to renal function;
- After 21d, all patients transferred to valganciclovir (900mg od) for 28d.

Primary endpoint: Successful treatment (defined as eradication of CMV viraemia at d 21, i.e. <600 viral copies/mL of plasma).

Secondary endpoints:

- Clinical assessment of CMV disease;
- Time to undetectable viraemia (<200 copies/mL);
- Viral load kinetics;
- Safety and tolerability.

Follow-up: At d 21 and 49.

Results

Table 30.9 Summary of results

| Primary endpoint | IV ganciclovir | Valganciclovir | <i>p</i> |
|------------------------------|----------------|----------------|----------|
| Viraemia eradication (d 21) | 48% | 45% | ns |
| Secondary endpoints | | | |
| Treatment success (d 21) | 80% | 77% | ns |
| Treatment success (d 49) | 84% | 85% | ns |
| Time to viraemia eradication | 19d | 21d | ns |
| Viral load half-life | 10d | 12d | ns |
| Adverse events | 64% | 70% | ns |

- A total of 46% had invasive CMV disease (49% of ganciclovir group; 43% of valganciclovir group). (See Table 30.9.)

Discussion

Oral valganciclovir was as effective as IV ganciclovir for the treatment of non-threatening (mild to moderate) CMV infection, with no significant differences in outcomes.

Problems

- Treatment was not blinded.
- The trial size was relatively small for a non-inferiority study.
- The majority of patients were kidney transplant recipients, limiting the general applicability of the conclusions for non-renal transplants.
- Overall, the percentage of patients clearing their viraemia (<50%) was less than expected (65%). This raises questions about the optimal length of treatment. Longer-term F/U on CMV recurrence and resistance would be informative.
- The conclusions cannot be extrapolated to include paediatric recipients of organ transplants.

Trauma and orthopaedics

Introduction 840

Developmental dysplasia of the hip: ultrasound screening 842

Dynamic hip screw: tip–apex distance in predicting failure 844

Hip fractures: hemiarthroplasty vs internal fixation 846

Femoral fracture: timing of surgery 848

Dislocation in revision total hip replacement 850

Magnetic resonance imaging assessment of knee injuries 852

Anterior cruciate ligament reconstruction: choice of graft 854

Partial meniscectomy for a meniscal tear and osteoarthritis 856

Cemented vs cementless unicompartmental knee replacement 858

External fixation of long bones: coated pins 860

Tibial fracture stabilization: type of nail 862

Mid-shaft clavicle fractures 864

Preventing sepsis: ultraclean air theatres 866

Introduction

The earliest evidence of orthopaedic principles in practice comes from the ancient Egyptian civilization. Egyptian mummies have been found with splints on broken bones, and wall paintings depicting crutches are known to be 5,000y old. Hippocrates (the Father of Medicine) wrote extensively on the treatment of fractures and dislocations, with detailed descriptions of reduction and splinting methodology, much of which is still valid today.

The word 'orthopaedics' derives from the Greek for 'straight child', and this reflects the origins of the specialty—addressing deformities in children. It was coined by Nicholas Andry with his text *Orthopaedia* of 1741. The Tree of Andry remains the symbol of orthopaedics throughout the world.

Jean André Venel is considered by many to be the father of orthopaedics, having opened the first orthopaedic hospital in 1780. Since then, the specialty has expanded to include trauma, joint disease, deformity correction, tumours, and conditions of the soft tissues of the musculoskeletal system.

Hugh Owen Thomas, a son of a bone setter, is considered as the founder of British orthopaedics. Among various inventions, the development of the 'Thomas splint' in 1875 is considered to be a key appliance (which is still widely used in the initial management of fractures of the femoral shaft) which contributed to significant reduction in mortality in the great wars. He never held a hospital appointment, preferring to treat patients in their own homes.

Sir John Charnley in the 1960s developed low-friction arthroplasty of the hip, revolutionizing the treatment of arthritis to the point where it seems that there are few joints left that cannot be replaced! He also developed the use of bone cement and was the first to realize the importance of ultraclean operating theatres and the use of laminar airflow.

The recent advances in biomechanics and biomaterials are resulting in new and potentially improved implants and procedures, often with more reliance on high-tech solutions. However, some new advances have resulted in disastrous outcomes, including the 3M hip and, more recently, the ongoing problems with metal-on-metal hips, which have become prominent in the past 5y. As it takes time for these complications to surface, many patients may be subject to the new technology and resulting consequences. Use of appropriate surrogate measures to assess the short-term *in vivo* performance of an implant is essential to help predict long-term clinical outcome. Radiostereometric analysis (RSA) and kinematic assessment are two such tools widely used in translational research and post-market surveillance in the field of joint replacement.

It is only with high-quality research and awareness that true advances can be demonstrated and failures averted at the earliest stage.

The principles of orthopaedics must remain to alleviate pain, correct deformity, and restore function, whatever technique is used.

Developmental dysplasia of the hip: ultrasound screening

Universal or selective screening of the neonatal hip using ultrasound? A prospective, randomised trial of 15,529 newborn infants.

AUTHORS: Holen K, Tegnander A, Bredland T et al.

REFERENCE: *J Bone Joint Surg* (2002) 84(B), 886–90.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the largest randomized trial to show that universal ultrasound (US) screening for neonatal hip dysplasia is unnecessary. It demonstrates the importance of proper screening for high-risk neonates and effective clinical examination of the hips post-partum in reducing cases of late presentation.

Impact

The use of US only for those neonates at high risk of dysplasia or with abnormal clinical examination remains an established and accepted standard.

Aims

This study was designed to assess whether universal screening of all neonates with hip US post-partum conferred a clear advantage over existing systems of only screening those neonates at high risk of having developmental dysplasia of the hip (DDH). The aim was to establish whether the additional time and expense of screening would reduce the rate of late diagnosis of DDH, which was three per 1,000 prior to the study.

Methods

Patients: 15,529 neonates at one European centre.

Inclusion criteria: All babies born between 1988 and 1992.

Groups:

- Universal screening group: Clinically examined on the first day of life, and all had hip US on around the third day after birth ($n = 7,840$);
- Selective screening group: clinically examined, and only those at high risk were examined with US ($n = 7,689$).

High-risk: Defined as having hip instability/doubtful stability on examination, family history of hip dysplasia, breech position, or foot deformities.

Clinical examination: Performed by a senior paediatrician and included Ortolani and Barlow tests. Repeated by orthopaedic surgeons at time of US.

Primary endpoint: Late detection, defined as the diagnosis of hip dysplasia, subluxation, or dislocation, in a baby >1 mo of age.

Follow up: Range 6–11y. Mean F/U 8.5y.

Results

Table 31.1 Summary of results

| | Examination and universal US (<i>n</i> = 7,840) | Examination and selective US (<i>n</i> = 7,689) |
|--|---|---|
| Had US | 7,489 (95.5%) | 872 (11.3%) |
| Late detection of DDH | 1 (0.13/1,000) (due to protocol failure) | 5 (0.65/1,000) |
| Rate of treatment (with Frejka pillow*) | 0.96% | 0.86% (ns) |

* Abducts and flexes the hip.

- No significant differences between groups for gender, birth rank, mean birthweight, or risk factors (e.g. breech position, family history, foot deformities, etc.) (see Table 31.1);
- Universal group:
 - Those who did not have US either were premature and transferred to intensive care or died perinatally;
 - The RR of late diagnosis of DDH was 0.21 for the universal group (not statistically different, $p = 0.2$).

Discussion

Previous trials had shown similar results but were not as large or as well designed. This study emphasized the importance of careful attention to the identification of those neonates at risk for DDH and the need for thorough clinical examination.

Problems

- Although this study had a large number of participants, there were only five positive results in one group and one in the other; this makes type 2 error possible.
- The study showed a dramatic reduction in late DDH presentation in both groups, suggesting that the study protocol itself improved the diagnosis rate significantly. Therefore, it could be suggested that the control group (selective screening) was not representative of current screening programme outcomes.

Dynamic hip screw: tip–apex distance in predicting failure

The value of the tip–apex distance in predicting failure of fixation of peritrochanteric fractures of the hip.

AUTHORS: Baumgaertner M, Curtin S, Lindskog D *et al.*

REFERENCE: *J Bone Joint Surg (Am)* (1995) **77**, 1058–64.

STUDY DESIGN: Retrospective review.

EVIDENCE LEVEL: 3.

Key message

First trial to describe the concept of the tip–apex distance (TAD). This study shows greatly reduced failure rates with dynamic hip screw fixation using a TAD of <25mm.

Impact

All dynamic hip screws are now performed with the aim of placing the screw in the centre of the head (in the anteroposterior and lateral planes) and minimizing the TAD.

Aims

The main mechanism of failure in dynamic hip screw fixation of intertrochanteric hip fractures is the so-called 'cut-out' of the screw. This is the collapse of the neck–shaft angle into varus, with subsequent extrusion of the hip screw, and is related to the position of the hip screw. The authors of this study proposed the TAD, the sum of the distance from the tip of the screw to the apex of the femoral head on an anteroposterior radiograph and the same distance on a lateral radiograph, as a description of the screw position. The aim of this study was to assess the value of the TAD in predicting cut-out of the lag screw.

Methods

Patients: 193 patients with 198 dynamic hip screws *in situ* at one centre in the USA.

Inclusion criteria: All patients with dynamic hip screw fixation of a peritrochanteric hip fracture:

- >3mo F/U;
- Either definitive union of the fracture or failure of fixation (which applied to all patients studied).

Groups: Broadly classified into following groups for analysis:

- TAD of ≤ 24 mm;
- TAD of ≥ 25 mm.

Primary endpoint: Screw cut-out.

Follow-up: Minimum of 3mo (mean F/U 13mo).

Results

Table 31.2 Summary of results

| Primary endpoint | TAD <25mm | TAD >25mm | p |
|------------------|---------------|-------------------|---------|
| Cut-out | No occurrence | 20.5% of patients | <0.0001 |

- 0% of screws with a TAD <25mm cut-out ($n = 0/120$) (see Table 31.2);
- 2% of screws with a TAD <30mm cut-out ($n = 3/150$);
- 27% of screws with a TAD >30mm cut-out ($n = 13/48$).

Cut-out:

- Average age of patients 9y older than those with intact fixation ($p = 0.02$);
- Commoner when unstable fractures were fixed ($p = 0.03$);
- Significantly higher when a 150° side plate was used ($p = 0.005$).

Failure:

- Non-significant trend to failure in hips with a poor reduction of the fracture ($p = 0.06$).

Discussion

Previous trials had shown failure rates for dynamic hip screw fixation of intertrochanteric hip fractures to be as high as 23%. This had been attributed to malposition, with the position having been defined by a complex division of the femoral head into zones. This was the first study to link cut-out to a specific measurement. This study showed cut-out rates of only 8%, showing the technique to be more reliable than previously thought.

Problems

- This was a retrospective study (studying this phenomenon as a prospective study with deliberate malpositioning would be highly unethical).
- There was only a short F/U period and a high rate of exclusion, due to incomplete data collection.

Hip fractures: hemiarthroplasty vs internal fixation

Hemiarthroplasty versus internal fixation for displaced intracapsular hip fractures in the elderly.

AUTHORS: Parker M, Khan R, Crawford J *et al.*

REFERENCE: *J Bone Joint Surg* (2002) 84(B), 1150–5.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This study provides definitive evidence for the benefits of hemiarthroplasty over internal fixation in patients 70–90y of age, with displaced intracapsular hip fractures.

Impact

Hemiarthroplasty is now confirmed as the operation of choice in displaced intracapsular hip fractures in all but the most elderly and frail patients. This has greatly reduced the need for revision surgery in this vulnerable group of patients.

Aims

Although previous studies had suggested arthroplasty to be associated with fewer of the later complications noted with internal fixation (such as displacement, non-union, or avascular necrosis), numbers were either small or the trials were not randomized. The study was designed to compare the intraoperative, post-operative, and delayed outcomes of reduction and screw fixation of subcapital hip fractures with those of hemiarthroplasty. With the early post-operative period being associated with complications dependent on blood loss and operative time, these factors were considered for each group. Long-term success was defined by avoidance of the need for further procedures and by survival.

Methods

Patients: 455 patients at one UK centre.

Inclusion criteria: All patients with displaced intracapsular hip fracture:

- Age >70y old;
- Fit for either surgical procedure;
- No RA or significant osteoarthritis (OA) of the hip;
- No chronic renal failure, Paget's disease of the bone, fracture through a tumour, or other metabolic bone disease;
- Surgery within 48h of the fracture, performed by the first author.

Groups:

- Internal fixation: Closed reduction and internal fixation with three parallel cancellous screws ($n = 226$);
- Uncemented hemiarthroplasty ($n = 229$).

Primary endpoint: Death.

Secondary endpoints:

- Requirement for further surgical procedure of the hip;
- Deep infection;
- Avascular necrosis of the hip (only applicable to the fixation group);
- Pain and function of the hip;
- Limb shortening.

Follow-up: At 1, 2, and 3y after surgery, with hip scores, residential status, and range of motion noted.

Results

Table 31.3 Summary of results

| Primary endpoint | Internal fixation (n = 223) | Hemiarthroplasty (n = 223) | p |
|----------------------------|--------------------------------|-------------------------------|------------|
| Cumulative survival | 0.74 | 0.73 | ns |
| Secondary endpoints | | | |
| Re-operation | 90 (56%) | 12 (5.4%) | Not stated |
| Deep infection | No cases | 2.6% | 0.03 |
| Avascular necrosis | 11 (4.9%) | 0 | ns |

Discussion

Fixation was associated with a shorter intraoperative time and less blood loss, compared with hemiarthroplasty. This did not translate to a difference in mortality. Over one-third of the fixation patients had evidence of fracture displacement or non-union at F/U. For patients between 70 and 90y of age, hemiarthroplasty had clear benefits, in terms of fewer complications and lower overall hospital stay (when readmissions for further surgery were considered). The lower complication rates with hemiarthroplasty in this elderly population were in keeping with the results of other studies and meta-analyses. (See Table 31.3.)

Problems

- The study F/U period was only up to 3y (although there is continued F/U of the cohort).
- The outcome of reoperation in the internal fixation group is not described in detail.

Femoral fracture: timing of surgery

Early versus delayed stabilization of femoral fractures. A prospective randomized study.

AUTHORS: Bone L, Johnson K, Weigelt J *et al.*

REFERENCE: *J Bone Joint Surg (Am)* (1989) **71**, 336–40.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First prospective study to show increased complications with delayed fixation of femoral fractures.

Impact

Early fixation of femoral fractures is now the standard throughout the Western world. Delays beyond 24h are avoided, if at all possible. The use of traction as initial treatment is no longer considered useful, even in multiply injured patients. This has greatly reduced the incidence of ARDS in trauma patients.

Aims

Fat embolism syndrome, leading to ARDS, is associated with a high mortality rate. Previous studies had noted lower rates in those fixed early; however, these were very prone to bias. This study aimed to assess whether time of fixation was independently associated with complication rates.

Methods

Patients: 178 patients at one centre in the USA.

Inclusion criteria: All cases of femoral shaft fracture:

- Age 16–75y;
- Seen within 24h of injury.

Exclusion criteria: Low-energy trauma and age >65y.

Groups: Injury severity score (ISS), calculated using the Hospital Trauma Index. Randomly assigned to early stabilization (ES, surgery within 24h) or late stabilization (LS, initial treatment with traction, then stabilized >48h post-injury). Randomized into:

- ES of isolated fracture femur (ISS <18) ($n = 42$);
- ES and multiple injuries (ISS >18) ($n = 46$);
- LS of isolated femoral fracture (ISS <18) ($n = 53$);
- LS and multiple injuries (ISS >18) ($n = 37$).

All associated injuries were treated as normal. Open fractures were washed out early, then either fixed (ES) or put back onto traction (LS).

Follow-up: Daily ABG measurements until $\text{PaO}_2 > 75\text{mmHg}$ (on room air).

Results

Table 31.4 Summary of results

| | <i>n</i> | Mean ISS | Mean hospital stay | Respiratory complications (abnormal ABG) | ARDS | PE/FE |
|-------------------|----------|-------------|--------------------------|--|------|-------|
| Early isolated | 42 | 11.3 | 7.3d | 5 (4) | 0 | 1/0 |
| Early multiple | 46 | 31.8 | 17.3d | 16 (15) | 1 | 0/0 |
| Late isolated | 53 | 11.5 | 10.4d | 14 (12) | 0 | 2/0 |
| Late multiple | 37 | 31.3 | 26.6d | 50 (33) | 6 | 1/2 |

ABG, arterial blood gas; FE, fat embolus; PE, pulmonary embolus.

- Other respiratory complications: seven cases of pneumonia and two cases of pulmonary dysfunction (see Table 31.4).

Discussion

The lack of specific and successful treatments for ARDS results in death in up to 50% of patients; therefore, prevention is a priority. This study was important, as it compensated for the non-randomized nature of previous trials, which had been flawed in their methodology (there was a tendency for the less severely injured to have early stabilization). This study showed an improvement in the respiratory health of those fixed early. This also helped to reduce inpatient stay costs.

Problems

- Unfortunately, there was no statistical analysis to determine the significance of the results.
- This study is now a little dated and showed the results of only one centre with the availability of all trauma services. In practice, it can be difficult to access general, orthopaedic, neurological, and plastic surgery services urgently; this makes it difficult to maintain this standard of approach.

Dislocation in revision total hip replacement

Do large heads (36 and 40 mm) result in reduced dislocation rates in a randomized clinical trial?

AUTHORS: Garbuz D, Masri B, Duncan C *et al.*

REFERENCE: *Clin Orthop Relat Res* (2012) **470**, 351–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A large femoral head (36 or 40mm) reduces dislocation rates in patients undergoing revision total hip arthroplasty (THA) at 5y F/U.

Impact

Following this clinical study, the use of large femoral heads should be considered in revision THA with intact abductors.

Aims

Dislocation after revision THA is a common complication. Large heads theoretically decrease the risk of dislocation in revision THA. This study investigated whether large femoral heads (36 and 40mm) result in decreased dislocation, compared to standard femoral head (32mm) in revision THA.

Methods

Patients: 184 across seven centres in North America.

Inclusion criteria:

- Revision of both acetabular and femoral components;
- Acetabular component with a minimum 50mm in diameter.

Exclusion criteria:

- Revision for recurrent dislocation;
- Use of cemented cup or constrained liner;
- Abductor deficiency.

Groups:

- Standard femoral head (32mm) ($n = 92$);
- Large femoral head (36 or 40mm) ($n = 92$).

Primary endpoint: Dislocation.

Secondary endpoints: QOL—WOMAC and SF36.

Follow-up: Mean for dislocation 5y (2–7); mean for QoL 2.2y (1.6–4).

Results

- Rate of dislocation 1.1% for large head group vs 8.7% for standard head group ($p = 0.035$);
- No difference in QoL between both groups, aside from SF36 mental component with the large head group scoring higher ($p = 0.043$);
- Mean time from surgery to dislocation 131d (range 3–507).

Discussion

The theoretical advantages of using large heads to prevent dislocation have not previously been proven clinically. This study showed that large heads had a significantly lower dislocation rate in revision THA with intact abductors. This may have been due to the increased head–neck ratio and jump distance or a mismatch between cup and head size.

Limitations

- A variety of surgical approaches to the hip were utilized.
- Patients with deficient abductors were excluded.

Magnetic resonance imaging assessment of knee injuries

Effectiveness of MR imaging in selection of patients for arthroscopy of the knee.

AUTHORS: Vincken P, ter Braak B, van Erkel A *et al.*

REFERENCE: *Radiology* (2002) 223, 739–46.

STUDY DESIGN: Prospective, multicentre, partially randomized.

EVIDENCE LEVEL: 2b.

Key message

In a general population, a combination of clinical examination and MRI is effective in the selection of patients for arthroscopy, thus reducing unnecessary invasive investigations.

Impact

These findings have increased the evidence base towards supporting non-invasive investigation of knee injuries.

Aims

MRI of the knee has a high degree of sensitivity and specificity for injury to individual intra-articular structures. More relevant to patient management is the correct selection of those patients who require arthroscopy, based on the overall appearance of the knee (composite diagnosis). This study aimed to evaluate MRI in patients with a high clinical suspicion of internal derangements, in order to identify those who required arthroscopic therapy.

Methods

Patients: 430 consecutively referred patients at three centres in The Netherlands.

Inclusion criteria:

- Age between 16 and 45y;
- ≥ 4 wk of pain, swelling, instability, and/or locking of the knee;
- High chance of internal derangement (based on physical examination).

Exclusion criteria:

- Known joint disease, history of locked knee, or previous knee surgery;
- Clinical diagnosis of retropatellar chondromalacia;
- Prior MRI or arthrographic diagnosis, or contraindication to either;
- Fracture.

Protocol: All patients underwent MRI within 2wk and were divided into:

- Normal;
- Abnormal but arthroscopic treatment not required;
- Abnormal with arthroscopic treatment required.

Composite diagnosis, based on the combination of the degree of individual structural damage. Half of the negative patients (normal and no treatment) underwent arthroscopy, and the other half were treated conservatively.

Results

- Patient demographics: mean age 30.6y; 69.5% ♂;
- Arthroscopy: indicated in 221 patients (undertaken in 200). Remaining patients randomized as: 105 for arthroscopy (93 undertaken) and 104 for conservative treatment;
- Correlation between positive (needed treatment) and negative MRI, and arthroscopy (see Table 31.5);
- Accuracy for composite diagnosis (needing arthroscopy) and individual injuries (see Table 31.6).

Table 31.5 Summary of results

| | | Arthroscopy | |
|-----|---|-------------|----|
| | | + | – |
| MRI | + | 179 | 21 |
| | – | 13 | 80 |

Table 31.6 Summary of results

| Injury | Composite diagnosis | Medial meniscus | Lateral meniscus | Anterior cruciate ligament rupture |
|-------------|---------------------|-----------------|------------------|------------------------------------|
| Sensitivity | 87 | 84 | 70 | 70 |
| Specificity | 88 | 94 | 95 | 95 |
| PPV | 89 | 90 | 81 | 60 |
| NPV | 86 | 91 | 91 | 97 |

Discussion

This paper looked at the usefulness of knee MRI in guiding management, rather than detecting structural damage. The higher sensitivity of composite diagnosis was explained by the fact that injuries to more than one individual structure led to a positive MRI result, and that injuries were often not isolated. This helped compensate for the relatively low sensitivity of MRI for individual structures. This study differs to previous ones in that it defines both its patient selection and the need for arthroscopy criteria.

Problems

- Only half the negative group underwent arthroscopy, introducing a verification bias. The authors compensated for this by doubling the figures from this group.
- The radiologist reporting the MRI was not blind to the clinical findings. The authors claimed this represented real practice more closely.

Anterior cruciate ligament reconstruction: choice of graft

A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft.

AUTHORS: Pinczewski L, Lyman J, Salmon L et al.

REFERENCE: *Am J Sports Med* (2007) 35, 564–74.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

This is the first randomized, prospective study into the 10y results of hamstring tendon and patellar tendon autograft for anterior cruciate ligament (ACL) reconstruction. The use of both autografts is supported, with no clear benefit of using either one over the other.

Impact

The reduction in donor site symptoms in hamstring tendon donors has led to a trend towards using hamstring graft, but both techniques remain popular. The positive results at 10y support the use of operative techniques to reconstruct the unstable knee.

Aims

There had been no previous prospective studies comparing long-term outcomes of the different types of ACL repair. Large numbers of papers had supported the use of either hamstring tendons or patellar tendon as graft. Previous comparative work had failed to separate the benefits and drawbacks of each technique. This study aimed to compare the functional results, re-rupture rate, and complication rates of the two common methods of ACL reconstruction.

Methods

Patients: 180 patients at one centre in Australia.

Inclusion criteria:

- Isolated, unilateral ACL injury;
- Symptomatic instability of the knee.

Exclusion criteria: History of previous cruciate ligament surgery.

Groups: Single surgeon operating on both groups:

- PT group: Bone patellar tendon bone autograft ($n = 90$);
- HT group: Ipsilateral, four-strand hamstring tendon autograft ($n = 90$).

Both groups were entered into a standardized, accelerated rehabilitation programme after surgery.

Results

- Both groups showed normal or near-normal knee function in 97% of patients;
- Pain on strenuous activity was commoner in the PT group ($p = 0.05$);
- Rates of graft rupture were equivalent in each group, with all ruptures associated with graft laxity at 2y after surgery;
- Kneeling pain ($p = 0.01$) and harvest site symptoms ($p = 0.001$) were commoner in the PT group;
- Radiographic evidence of OA was commoner in the PT group ($p = 0.05$).

Discussion

It was possible to get excellent results with hamstring or patellar tendon reconstruction of the ACL. The authors recommended the use of hamstring autograft, because of the reduction in donor site morbidity and radiographic signs of OA. It may be of significance to avoid the use of the patella tendon in patients whose work involves kneeling down. It is of particular note that the hamstring graft group did not suffer noticeable ill effects associated with the loss of strength in deep flexion of the knee, first noted in 1996 (*J Jap Clin Sports Med Assoc* (1996) 6, 681–6) and again shown in the intervening years.

Problems

- The study was not blinded for the outcome measures; this would be very difficult, because of the differences in scars in each group.
- This study represented the results of a very experienced surgeon in a specialist centre and did not include the 'learning curve' for the change to hamstring graft that other surgeons would have to go through.
- Frank OA takes many years to develop, and yet longer F/U is required to establish if the increase in radiographic signs of OA in the patella tendon group leads to increased risk of painful arthritis.

Partial meniscectomy for a meniscal tear and osteoarthritis

Surgery versus physical therapy for a meniscal tear and osteoarthritis.

AUTHORS: Katz J, Brophy R, Chaisson C et al.

REFERENCE: *N Engl J Med* (2013) **368**, 1675–84.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There were no significant differences between the study groups in functional improvement at 6mo; however, 30% of the patients who were assigned to physiotherapy alone underwent surgery within 6mo.

Impact

This study supports the use of either treatment modality in the management of symptomatic meniscal damage with concurrent OA.

Aims

Recent studies have shown limited benefit of arthroscopy in knee OA. A symptomatic meniscal tear is a common indication for arthroscopy in patients with concurrent OA. This study assessed outcomes for arthroscopic partial meniscectomy in symptomatic patients with a meniscal tear and knee OA, compared to those who underwent physiotherapy alone.

Methods

Patients: 351 across seven tertiary hospitals in the USA.

Inclusion criteria: Symptomatic patients aged >45 with meniscal tear and mild to moderate OA on imaging (MRI)

Groups:

- Surgery (arthroscopic partial meniscectomy) and physical therapy ($n = 174$);
- Physical therapy (control) ($n = 177$).

Primary endpoint: WOMAC score.

Secondary endpoints: KOOS and SF36 scores.

Follow-up: 3, 6 (1°), and 12mo.

Results

- At 6mo, in the ITT analysis, mean improvement in the WOMAC score was 20.9 (95% CI 17.9–23.9) in the surgical group and 18.5 (95% CI 15.6–21.5) in the physiotherapy group;
- At 6mo, 51 patients (30%) who were assigned to physiotherapy alone crossed over and underwent surgery, and nine patients (6%) assigned to surgery had not undergone surgery;

- The results at 12mo were similar to 6mo;
- The number of adverse events did not differ significantly between the groups.

Discussion

There was no significant difference in the magnitude of functional and pain improvement between both groups at 6 and 12mo. This echoes a previous smaller study. Although both treatment modalities have been shown to be effective for symptomatic meniscal tear in concurrent OA, the authors recommend that physiotherapy be trialled for 6mo, and, if no significant improvement is seen, then arthroscopy meniscectomy can be undertaken.

Limitations

- Only 26% of eligible patients enrolled—selection bias.
- 30% cross-over rate at 6mo from physiotherapy to surgery.
- Study was not blinded, as a sham procedure was not feasible.

Cemented vs cementless unicompartmental knee replacement

Improved fixation in cementless unicompartmental knee replacement: five-year results of a randomized controlled trial.

AUTHORS: Pandit H, Liddle A, Murray D *et al.*

REFERENCE: *J Bone Joint Surg (Am)* (2013) **95**, 1365–72.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Cementless fixation provides improved fixation at 5y, compared to cemented fixation, in mobile-bearing unicompartmental knee replacement (UKR), maintaining equivalent or superior clinical outcomes with a shorter operative time and no increase in complications.

Impact

Cementless fixation of UKR is encouraged in the treatment of symptomatic end-stage anteromedial OA.

Aims

UKRs typically have higher revision rates, compared to total knee replacements (TKRs). Common reasons for revision include aseptic loosening and pain. These can potentially be overcome by improving fixation quality. The aim of this study was to compare the quality of fixation (as demonstrated by radiolucency) and functional outcomes in cemented and cementless designs of the Oxford UKR.

Methods

Patients: 62 patients (63 knees) at one UK centre.

Inclusion criteria:

- Symptomatic end-stage anteromedial OA;
- Criteria for Oxford UKR (intact ACL, full-thickness medial cartilage loss, full-thickness lateral compartment cartilage preservation).

Exclusion criteria:

- Previous ACL surgery or osteotomy.

Groups:

- Cementless Oxford UKR ($n = 30$);
- Cemented Oxford UKR ($n = 32$).

Primary endpoint: Radiolucency.

Secondary endpoints: Functional scores (Oxford Knee Score, American Knee Society Score, Tegner Activity score).

Follow-up: Post-operatively, 6mo, 1y, and 5y.

Results

- Nine complete radiolucencies in the cemented group, and zero in the cementless group ($p < 0.001$);
- Significantly more tibial radiolucencies in the cemented group (20/30 vs 2/27, $p < 0.001$);
- There were no revisions;
- Knee Society function scores were higher in the cementless group ($p = 0.003$);
- Mean operative time was 11min shorter in the cementless group ($p = 0.029$).

Discussion

This study demonstrates that cementless fixation in Oxford UKR is associated with a significantly reduced incidence of radiolucencies, compared to cemented fixation, at 5y, with equivalent or superior functional outcomes. Both groups, however, showed no evidence of loosening or of radiolucency progression between 1 and 5y.

Limitations

- Small study and not powered to detect change in functional scores;
- Single-centre study from designers.

External fixation of long bones: coated pins

Hydroxyapatite-coated Schanz pins in external fixators used for distraction osteogenesis.

AUTHORS: Pommer A, Muhr G, David A.

REFERENCE: *J Bone Joint Surg (Am)* (2002) **84**, 1162–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Coating of external fixator pins significantly reduces the rates of loosening and infection. These should be the implants of choice in distraction osteogenesis and for other procedures requiring prolonged fixation.

Impact

Hydroxyapatite (HA)-coated pins are now used in limb reconstruction to improve fixation to bone.

Aims

One of the commonest complications of external stabilization during limb reconstruction is loosening of the fixator pins. This dramatically increases the chances of infection, which can have devastating consequences. HA had been shown to improve fixation of bone to a variety of other implants in human and animal models. This study aimed to compare the pull-out strength, loosening rates, and infection rates of uncoated titanium pins with HA-coated pins.

Methods

Patients: 46 patients at one centre in Germany.

Inclusion criteria: All patients with distraction osteogenesis in the 2y study period.

Groups:

- Control group: AO/ASIF 3.8mm-diameter titanium Schanz pins ($n = 23$);
- Experiment group: identically shaped steel pins coated with a 50-micrometer HA layer ($n = 23$).

Primary endpoint: Need to replace the external fixator pin.

Secondary endpoints:

- Radiological loosening: Presence of a continuous radiolucent line on both sides of the screw on the near cortex;
- Clinical loosening: Pain, erythema, warmth, swelling, or discharge at the pin site;
- Pin site infection: Assay from secretions swabbed from the pin site;
- Significant infection: Acute bone marrow infection;
- Extraction torque at the time of removal.

Results

- Total of 334 pins inserted;
- Average age 39y (914.1, range 18–61y) (see Table 31.7).

Table 31.7 Summary of results

| Primary endpoint | Uncoated pins (23 patients, 169 pins) | HA-coated pins (23 patients, 165 pins) | <i>p</i> |
|----------------------------|--|---|----------|
| Pins needing replacing | 22 | 0 | <0.001 |
| Secondary endpoints | | | |
| Loosening | 22 | 0 | <0.001 |
| Pin site infection | 20 | 0 | <0.001 |
| Significant infection | 1 | 0 | ns |
| Pull-out torque | 0.10 N-m | 0.43 N-m | <0.001 |

N-m, Newton metre.

Discussion

Earlier trials had attempted to reduce the micromotion of pins in the bone by pre-stressing the pins or using different pin designs; these had not been successful. This study used HA-coated pins (HA was integrated into the cortices around the whole diameter of the pins), allowing for more effective dissipation of all forces, thus reducing the peak force per unit area. The significant differences observed in this study showed that HA-coated pins reduced both morbidity and hospital stay for patients.

Problems

- Limited numbers.
- The control group used titanium pins, and the experimental group used stainless steel. These materials have different stiffness that could affect the strength of anchoring.
- The pins were not standardized for depth of insertion and contact area with the cortical bone.
- The study did not address whether this was a cost-effective improvement.

Tibial fracture stabilization: type of nails

Randomized trial of reamed and unreamed intramedullary nailing of tibial shaft fractures (SPRINT).

AUTHORS: Bhandari M, Guyatt G, Tornetta P *et al.*

REFERENCE: *J Bone Joint Surg (Am)* (2008) **90**, 2567–78.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Delaying reoperation for non-union at least 6mo may substantially decrease the need for reoperation. The use of reamed IM nails in closed fractures appears to produce better outcomes. It is unclear which nailing technique is best in open fractures.

Impact

This study supports the use of reamed nailing in closed fractures.

Aims

Tibial shaft fractures are extremely common injuries, and treatment with intramedullary nailing has been shown to be effective. The choice of which technique to use (reamed compared to unreamed) is controversial, however. This multicentre, blinded, randomized study compared the effects of reamed vs unreamed intramedullary nailing for tibial fractures.

Methods

Patients: 1,319 patients across 29 sites in North America and The Netherlands.

Inclusion criteria:

- Open or closed tibial shaft fracture;
- Skeletally mature.

Groups:

- Reamed intramedullary nail ($n = 671$);
- Unreamed intramedullary nail ($n = 648$).

Primary endpoint: Reoperation and autodynamization, including composite from: bone grafting; implant exchange/removal; debridement for infection; dynamization; removal of broken screws; haematoma drainage; fasciotomy.

Follow-up: 12mo.

Results

Table 31.8 Summary of results

| Primary event | Reamed | Unreamed | RR | p |
|-----------------|--------------|--------------|------|-----------|
| Closed fracture | 45/416 (11%) | 68/410 (17%) | 0.67 | 0.03 |
| Open fracture | 60/206 (29%) | 46/194(24%) | 1.27 | 0.16 (ns) |

- The difference in primary outcome events between both groups for closed fractures was primarily due to different rates of autodynamization (see Table 31.8);
- A total of 57 (4.6%) patients underwent exchange nailing or bone grafting for non-union;
- A total of 14 adverse events occurred in the reamed group, compared to four in the unreamed group ($p = 0.03$). Blinded adjudicators classified all deaths as unrelated to the nailing procedure.

Discussion

This study supports the use of reamed nailing in closed fractures, due to a smaller number of primary events occurring in this group, particularly dynamization. However, it has not been determined which technique is best in managing open fractures. By delaying reoperation for non-union until at least 6mo after index surgery, this study had a lower rate of reoperation, compared to previous studies. This is likely because of the increased time given for fracture healing to occur.

Problems

- Surgeons were more experienced with reamed nailing.
- Surgeons were not blinded—87% believed that reaming was superior, potentially leading to a different threshold for reoperation.

Mid-shaft clavicle fractures

Nonoperative treatment compared with plate fixation of displaced mid-shaft clavicle fractures.

AUTHORS: Canadian Orthopaedic Trauma Society.

REFERENCE: *J Bone Joint Surg (Am)* (2007) **89**, 1–10.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Operative plate fixation of displaced mid-shaft clavicle fractures results in improved functional and patient-related outcomes and higher union rates, compared to non-operative management, at 1y.

Impact

There is increasing popularity in managing mid-shaft clavicle fractures with plate fixation, particularly in high-functioning patients.

Aims

Clavicle fractures, even when significantly displaced, have traditionally been treated conservatively. Recent studies have shown a high prevalence of symptomatic malunion/non-union when non-operative management is undertaken. The purpose of this trial was to compare outcomes (patient- and surgeon-related) from operative vs non-operative management of completely displaced mid-shaft clavicle fractures.

Methods

Patients: 132 across eight hospitals in Canada.

Inclusion criteria:

- Completely displaced mid-shaft (middle 1/3) clavicle fracture;
- Age 16–60.

Exclusion criteria:

- Open/pathological fracture;
- Head injury;
- Upper extremity fracture distal to shoulder.

Groups:

- Operative fixation with a plate ($n = 67$);
- Non-operative management with a sling ($n = 65$).

Primary endpoint: Functional and patient-related scores (Constant and DASH).

Secondary endpoints: Time to radiographic union; complications—non-union, malunion, infection, hardware-related.

Follow-up: 6wk, and 3, 6, and 12mo.

Results

- Constant and DASH scores were significantly improved in the operative fixation group at all time points ($p = 0.001$ and $p < 0.01$, respectively);
- Mean time to radiographic union was 28.4wk in the non-operative group vs 16.4wk in the operative group ($p = 0.001$);
- Two non-unions in the operative group, compared with seven in the non-operative group ($p = 0.042$);
- Symptomatic malunion developed in nine patients in the non-operative group, and in none in the operative group ($p = 0.001$);
- Most complications in the operative group were hardware-related (five patients had local irritation and/or prominence of the hardware; three had a wound infection, and one had mechanical failure);
- Patients in the operative group were more likely to be satisfied with the appearance ($p = 0.001$) and the shoulder in general ($p = 0.002$).

Discussion

This study demonstrated that operative plate fixation of displaced mid-shaft clavicle fractures in active individuals resulted in better functional outcomes and union rate, compared to sling treatment. Further research is needed to determine whether plate fixation is the optimal operative treatment modality for these fractures.

Problems

- Complications in the operative group would likely be missed outside the trial setting, due to lack of F/U.
- Re-intervention rate (e.g. for hardware removal) would be expected to increase with greater F/U.

Preventing sepsis: ultraclean air theatres

Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study.

AUTHORS: Lidwell O, Lowbury E, Whyte W et al.

REFERENCE: *BMJ* (1982) 285, 10–14.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

First RCT to show a significant reduction in sepsis in total hip and total knee arthroplasties performed in ultraclean air theatres, compared with conventionally ventilated 'plenum' theatres. It also links the use of parenteral antibiotics to a reduction in infection rates.

Impact

Ultraclean air systems are now the standard in joint replacement practice. The British Orthopaedic Association recommends that all joint replacements should be carried out in ultraclean air theatres.

Aims

Deep sepsis is a significant cause of failure in total joint replacement and usually requires two-stage revision surgery to resolve the infection. This study was designed to elucidate the relationship between deep sepsis and theatre design. It sought to relate the numbers of deep infections to bacterial counts in air samples and to further relate the bacterial counts to the use of plenum theatres, ultraclean air theatres, and ultraclean air theatres in which the surgeons wore body exhaust suits.

Methods

Patients: 8,136 operations at 15 British and four Swedish orthopaedic units.

Inclusion criteria: 1° hip or knee arthroplasty:

- Control theatres ventilated by a positive pressure air supply (plenum theatre);
- Each surgeon operated in both conventional and ultraclean theatres;
- Air samples taken during the operations in each theatre type.

Groups: Divided in a 2:1:1 ratio (for logistical reasons):

- Plenum theatre (control) ($n = 4,133$);
- Ultraclean air theatre with surgeons wearing conventional gowns ($n = 1,789$);
- Ultraclean air theatre with surgeons wearing exhaust suits ($n = 2,133$).

Primary endpoint: Bacterial infection within the joint associated with clinically apparent tissue damage.

Secondary endpoints: Possible sepsis, based on the following criteria:

- Isolation of potentially pathogenic microorganisms from the joint;
- Raised ESR in patients who had previously normal rates;
- Suggestive histological findings;
- Abnormal X-ray;

- Abnormal pain;
- Fever at the time of repeat operation.

Follow-up: Up to 1y after the last patient had entered the trial in each centre (mean F/U 2–2.5y).

Results

Table 31.9 Summary of results

| Primary endpoint | Conventional | Ultraclean | p |
|---------------------------|--------------|------------|--------|
| Sepsis or probable sepsis | 1.5% | 0.6% | <0.001 |
| Secondary endpoint | | | |
| Possible sepsis | 0.5% | 0.5% | ns |

Table 31.10 Summary of results

| | No antibiotics | | Antibiotics | | p |
|------------|----------------|------------|----------------|------------|--------|
| | Operations (n) | Septic (n) | Operations (n) | Septic (n) | |
| Control | 1,161 | 39 | 2,969 | 24 | <0.001 |
| Ultraclean | 1,060 | 13 | 2,863 | 10 | <0.01 |

Discussion

Previous trials had demonstrated infection rates in 1° hip and knee arthroplasty of up to 10%. This study revealed a 2.6-fold decrease in deep sepsis in patients operated on in ultraclean theatres. This was further broken down into a 2-fold decrease in ultraclean theatres alone, and a 4-fold decrease in ultraclean theatres combined with exhaust suits. This supports the theory that airborne bacteria are a significant cause of infection in arthroplasty surgery. The study also revealed a 3-fold reduction in infection rates among those patients receiving parenteral antibiotics. (See Tables 31.9 and 31.10.)

Problems

- There were a multitude of different theatre designs used to obtain appropriate numbers, rather than a standard design for one conventional and one ultraclean theatre type.
- The study did not control for the use of parenteral antibiotic prophylaxis or the use of antibiotic-laden cement. There was an association found between reduced infection risk and receipt of antibiotics, but this was not randomized so could not be properly assessed.
- The actual rate of use of exhaust suits remains low, because of comfort problems experienced by operating surgeons.

Urology

Introduction 870

Stress urinary incontinence: tension-free vaginal tape 872

Benign prostatic hyperplasia: medical treatment 874

Erectile dysfunction: sildenafil 876

Renal colic: imaging 878

Renal colic: analgesia 880

Renal colic: treatment of obstructive pyelonephritis 882

Renal calculi: nephrolithiasis 884

Prostate cancer: prevention with finasteride 886

Prostate cancer: hormone and radiotherapy 888

Prostate cancer: active surveillance vs radical prostatectomy 890

Bladder cancer: assessment of haematuria 892

Bladder cancer: post-operative intravesical therapy 894

Introduction

The EBM roots of urology are deep. The removal of stones from the urinary bladder is an ancient art, based upon a single piece of evidence—that pain from the bladder is only cured by removal of the stone. The devices used to remove stones bear testimony to the ingenuity of those who designed and improved them, based upon simple evidence of the newer versions working better. From the early days of ureteric tongs to crush stones, 1824 saw the first successful lithotripsy with the ‘trilabium’—a device with three claws to hold a stone, and a drill to fragment it. Such innovations were refined, based upon improved clinical outcomes; as rod lenses eventually entered mainstream urological practice, blind stone fragmentation was replaced by safer visual stone identification and removal.

Modern urology has been at the forefront of EBM. The extracorporeal lithotripter is a prime example of the development of a new technique from laboratory to patient. Evolution through *in vitro* experiments followed by *in vivo* animal and human experiments has led to the development of the newer generations of machines, capable of being used without anaesthesia. These are very different from the prototype HM-3 (human-model-3 machine) that required both an anaesthetized patient and a ready water bath. Evidence-based innovations in urology are not confined to minimally invasive surgery. Radical prostatectomy is still considered an important option for early prostate cancer. Doyens, like Patrick Walsh, have refined the technical aspects of this highly complex operation by documenting each step precisely and objectively analysing outcomes. As a result, today’s urologists have the benefit of extensive anatomical knowledge of the pelvis, urinary sphincter, and neurovascular bundles. The emergence of exciting technological innovations, such as laser and robotic surgery, continues to attest to the role of evidence-based practice in urology.

Continuing changes in medical practice are inevitable. With the need to ensure that the patient remains the focal point in the minds of those who bring about such changes, EBM has become the safety net. Following on from the studies presented here, subsequent meta-analyses allow validation of individual study findings. When appropriately interpreted (and in the context of local cost implications), the use of evidence will hopefully ensure that any positive developments remain changes for the benefit of patients, rather than passing changes in fashion.

Stress urinary incontinence: tension-free vaginal tape

A multicenter study of tension-free vaginal tape (TVT) for surgical treatment of stress urinary incontinence.

AUTHORS: Ulmsten U, Falconer C, Johnson P *et al.*

REFERENCE: *Int Urogynaecol J* (1998) 9, 210–13.

STUDY DESIGN: Prospective, open, cohort.

EVIDENCE LEVEL: 2b

Key message

First prospective RCT to show tension-free vaginal tape (TVT) insertion to be an effective surgical procedure for the treatment of stress urinary incontinence.

Impact

TVT has become an important procedure in the management of these patients. However, more recent reports have highlighted the risks associated with meshes, including erosion, infection, and sexual dysfunction.

Aims

Some studies have reported urinary continence rates in women to be as high as 52%. Stress incontinence is thought to be due to laxity of the vagina or its supporting ligaments. Colposuspension (surgically elevating the bladder neck) was a commonly used treatment, with 1y cure rates of up to 95%. TVT is a form of low-tension urethropexy, involving the use of a plastic sheath-covered polypropylene mesh. Early studies had proposed TVT sling insertion to be a quick and simple procedure for the treatment of stress urinary incontinence. This multicentre study aimed to further assess the safety and efficacy of this procedure.

Methods

Patients: 131 women at six centres in Scandinavia.

Inclusion criteria:

- Demonstrable genuine stress urinary incontinence (at least grade II on the Ingelman–Sundberg scale);
- Symptoms for several years (mean 8.3y);
- No previous surgery for incontinence;
- Included, irrespective of high or low urethral pressure.

Follow-up:

- At 2, 6, and 12mo. Post-operative F/U was standardized and included urodynamic assessment, whenever possible;
- ‘Significant improvement’ defined by negative stress test (repeated cough provocation with a filled bladder), >90% improvement in modified QoL assessment, >75% improvement in VAS, and <10g of leakage on 24h pad test;
- ‘Cure’ defined as no post-operative urine leakage.

All procedures performed using standardized technique, under local anaesthesia, with plastic sheath covered with Prolene®/Ethicon® TVT; 90% day cases.

Results

Baseline:

- Mean age 53y (35–88); mean parity 2 (0–5);
- No women showed signs/symptoms of prolapse;
- All post-menopausal women were on systemic or local therapy;
- Mean operating time 28min (range 19–41);
- Cure: 119 patients (91%; pad testing confirming 90% continence);
- Significant improvement: nine patients (7%). Remainder did not have full bladder control but did demonstrate reduced leakage;
- Complications: 1× bladder perforation, 1× wound infection, 3× acute urinary retention requiring short-term catheterization, and 1× retropubic haematoma (spontaneously resolved). No tape rejection.

Discussion

This multicentre study confirmed the safety and efficacy of TVT as a minimally invasive surgical treatment method for stress urinary incontinence. It also confirmed that the procedure could be performed safely as a day case under local anaesthesia, with low complication rates, even with less experienced operators. However, more recent reports have identified longer-term complications, including erosion, infection, and QoL implications on sexual function.

Problems

- Short F/U period, although the authors' earlier data had suggested high 'cure' rates at 3y. Definitive long-term outcome data are required.
- The aim of this study was to determine safety and efficacy, rather than to compare TVT with other surgical techniques; therefore, more comparative data with other techniques are needed (e.g. with Burch colposuspension).

Benign prostatic hyperplasia: medical treatment

MTOPS (Medical Therapy Of Prostatic Symptoms): The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia.

AUTHORS: McConnell J, Roehrborn C, Bautista O et al.

REFERENCE: *N Engl J Med* (2003) 349, 2387–98.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

A combination of doxazosin and finasteride is better than either drug alone in preventing the progression of obstructive (lower tract) urinary symptoms in benign prostatic hyperplasia (BPH).

Impact

Combination therapy has since become part of the first-line treatment protocol for BPH, especially for prostate volumes >40mL. Newer agents, such as tamsulosin, have since entered mainstream practice.

Aims

Previous studies had shown the effectiveness of α -blockers and finasteride in relieving the lower urinary tract symptoms (LUTS) of BPH, with no benefits seen from combined treatment. As BPH is progressive, this study aimed to determine whether doxazosin and finasteride, either alone or in combination, could also delay or prevent BPH clinical disease progression.

Methods

Patients and groups: 3,047 men (116 for a pilot study, 2,931 for the full study) at 17 centres in the USA.

Inclusion criteria:

- Age >50y, with no prior medical/surgical treatment;
- American Urological Association (AUA) symptom score: 8–30;
- Max urinary flow rate (Q_{\max}) of 4–15mL/s and voided volume >125mL.

Exclusion criteria:

- Prostate-specific antigen (PSA) >10ng/mL;
- Supine BP <90/70mmHg.

Groups:

- Placebo ($n = 737$);
- Doxazosin ($n = 756$);
- Finasteride ($n = 768$);
- Combination therapy ($n = 786$).

Primary endpoints:

- Overall clinical disease progression;
- Increase in AUA score >4 (commonest recorded);
- Acute urinary retention (AUR);
- Renal insufficiency (2° BPH): creatinine increase >50% of baseline;
- Recurrent urinary tract infections (UTIs) (>2/y) or hygienically unacceptable incontinence.

Secondary endpoints:

- Changes over time in AUA score, Q_{\max} , PSA, and prostate volume;
- Need for surgical intervention (e.g. transurethral resection of the prostate (TURP), laser, open prostatectomy).

Follow-up: Recruitment from 1993 to 1998. Mean F/U 4.5y.

Results

Table 32.1 Summary of results

| | Primary outcome events | NNT | NNT (PSA >4.0ng/mL) (20% men) | NNT (prostate volume >40mL) (30% men) | RR of developing increase in AUA >4 |
|-------------|------------------------|------|-------------------------------|---------------------------------------|-------------------------------------|
| Placebo | 128 | — | — | — | — |
| Doxazosin | 85 | 13.7 | — | — | 45% decrease ($p < 0.001$) |
| Finasteride | 89 | 15.0 | 7.2 | 7.2 | 30% decrease ($p = 0.02$) |
| Combination | 49 | 8.4 | 4.7 | 4.9 | 64% decrease ($p < 0.001$) |

NNT, number needed to treat to prevent one instance of disease progression.

- AUR events: 18 (placebo) vs 6 (finasteride, $p = 0.009$) and 4 (combination, $p < 0.001$). Doxazosin delayed time to AUR but did not decrease incidence ($p < 0.2$);
- Need for invasive treatment: Finasteride and combination decreased need by 64%. No change with doxazosin;
- Symptom score: 4y mean decrease in score 4.9 (placebo) vs 6.6 (doxazosin, $p < 0.001$), 5.6 (finasteride, $p < 0.001$), and 7.4 (combination, $p < 0.001$);
- Median prostate volume change: 24% decrease (placebo and doxazosin), 19% decrease (finasteride and combination);
- Major SEs: Doxazosin (dizziness, postural hypotension, asthenia), finasteride (erectile dysfunction, decreased libido, abnormal ejaculation);
- Clinical progression: Compared with placebo, doxazosin decreased risk by 39% ($p < 0.001$), finasteride by 34% ($p = 0.002$), and combination by 66% ($p < 0.001$) (see Table 32.1).

Discussion

Although both drugs alone showed a significant decrease in clinical progression, combination treatment was significantly better than monotherapy in reducing the incidence of AUR and need for invasive treatments.

Problems

- Large numbers discontinued, primarily due to adverse SEs: 18% (combination), 24% (doxazosin), and 27% (finasteride).
- Breast cancer diagnosed in four men using finasteride/combination treatment; this is a higher figure than reported by other trials (e.g. PCPT).
- Two previous 1y trials had shown no benefit of combination therapy over monotherapy (Veterans Affairs (*N Engl J Med* (1996) **335**, 533–9); PREDICT (*Curr Urol Rep* (2003) **4**, 267–8)). Difference likely to be due to consideration of larger prostate volumes.

Erectile dysfunction: sildenafil

Oral sildenafil in the treatment of erectile dysfunction.

AUTHORS: Goldstein I, Lue T, Padma-Nathan H *et al.*

REFERENCE: *N Engl J Med* (1998) **338**, 1397–404.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Oral sildenafil is effective in the treatment of erectile dysfunction (ED).

Impact

Sildenafil (Viagra®) became the first mainline pharmacological therapy for ED. Other phosphodiesterase (PDE) inhibitors have since been developed.

Aims

No effective oral treatment for ED was available at the time of this study. Sildenafil, a selective inhibitor of cyclic guanosine monophosphate (GMP)-specific PDE type 5, assists with erections in response to sexual stimulation. It is effective for 3–5h and is absorbed to maximum plasma levels within 1h. This study aimed to evaluate the safety and efficacy of sildenafil with variable dosing regimes.

Methods

Patients: 532 patients from 37 centres in the USA.

Inclusion criteria:

- Men aged ≥ 18 y;
- ED of organic, psychogenic, or mixed cause.

Exclusion criteria:

- Penile anatomical defects or spinal cord injury;
- 1° diagnosis of another sexual disorder;
- Major psychiatric disorder or alcohol/drug abuse;
- Poorly controlled DM;
- Active peptic ulcer;
- MI/stroke in the past 6mo, or ongoing nitrate use.

Groups:

- Placebo;
- Oral sildenafil (dose of 25, 50, or 100mg);
- Grouped as above, for two sequential, double-blind studies:
 - 1st = 24wk dose response study ($n = 216$ placebo, 316 sildenafil);
 - 2nd = 12wk flexible dose escalation study ($n = 166$ placebo, 163 sildenafil).

Primary endpoint: Efficacy assessed using the International Index of Erectile Function (IIEF) and event log at regular intervals, assessing the ability to achieve and maintain an erection sufficient for intercourse.

Follow-up: Regular F/U throughout duration of 24wk study, including 15-question IIEF questionnaire: 1 (never/poor) to 5 (always/good) scale.

Results

Table 32.2 Summary of results

| | Dose response | | Dose escalation | |
|---|----------------------|--|----------------------|--|
| | Placebo (n = 216) | Sildenafil (n = 316) | Placebo (n = 166) | Sildenafil (n = 163) |
| Mean age (y) (range) | 57 (20–79) | 58 (24–87) | 59 (31–81) | 60 (26–79) |
| ED, mean duration (y) | 3.2 | 3.2 | 4.7 | 5.0 |
| ED, organic causes (n) | 77 | 78 | 63 | 55 |
| Completed study | 180 (83%) | 285 (90%) | 153 (92%) | 154 (94%) |
| Stopped due to SEs | 1 (<1%) | 1 (1%) | – | 1 (<1%) |
| Stopped due to poor response | 11 (5%) | 5 (2%) | – | 1 (<1%) |
| Improvement in frequency of penetration (all men) | 5% | 25mg = 60% 50mg = 84% 100mg = 100% | 10% | 95% |
| Improvement in maintenance of erection post-intercourse | 24% | 25mg = 121% 50mg = 133% 100mg = 130% | 13% | 140% |
| Completion dose | – | – | – | 25mg = 2% 50mg = 23% 100mg = 74% |

- A total of 92% (n = 207) in the dose escalation study completed an additional 32wk of sildenafil, with only 2% (n = 4) withdrawing due to SEs (see Table 32.2).

Discussion

Sildenafil was safe, well tolerated, and increasingly effective with higher doses (improved frequency of penetration and maintenance of erection), irrespective of the underlying cause of ED. The main SEs were transient headache, flushing, dyspepsia, and rhinitis. Visual disturbances (PDE-6-related) were transient and dose-related, lasting up to a few hours.

Problems

- The study relied on patient self-reporting of successful sexual function, prone to an element of subjective bias.
- Drug company-funded study; however, unclear if this had any bearing on the results.

Renal colic: imaging

One year's clinical experience with unenhanced spiral computed tomography for the assessment of acute loin pain suggestive of renal colic.

AUTHORS: Greenwell T, Woodhams S, Denton E *et al.*

REFERENCE: *BJU Int* (2000) **85**, 632-6.

STUDY DESIGN: Prospective cohort.

EVIDENCE LEVEL: 2b.

Key message

Unenhanced spiral CT allows a rapid, contrast medium-free, anatomically accurate diagnosis of urinary tract calculi and, in the present series, had a sensitivity of 98% and a specificity of 97%. CT provided an alternative diagnosis in 6% of patients.

Impact

CT KUB (kidney, ureter, bladder) is now the first-line investigation for renal colic in most centres across the UK. The advantages must be weighed against the greater radiation dose of unenhanced spiral CT than with three-film intravenous urography (IVU), and, in practice, the requirement for a radiologist to interpret routine axial scans.

Aims

Since its introduction in 1923, IVU had been the gold standard for investigating acute loin pain suggestive of urinary tract calculi. However, the advantages of CT (with regard to sensitivity and specificity) were undisputed. The advantage of being contrast-free (thus avoiding the 2% incidence of severe adverse reaction, and the incidence of renal dysfunction attributed to IV iodinated contrast media) and the ability to diagnose alternative pathologies prompted this trial of unenhanced spiral CT as a first-line radiological investigation in suspected renal colic.

Methods

Patients: 116 patients (81 men, 35 women) at one centre in the UK.

Inclusion criteria: All patients attending a hospital ED with acute loin pain suggestive of renal colic.

Protocol:

- All patients underwent unenhanced spiral CT; IVU only performed if spiral CT was unhelpful;
- Unenhanced spiral CT conducted between 8.30 a.m. and 9 p.m.; patients presenting outside this period were managed symptomatically and underwent spiral CT the following morning;

- Patients suspected clinically of having an infected obstructed system were exempt from this protocol;
- Diagnosis of urinary tract calculi on unenhanced spiral CT, based on the identification of a calculus in the urinary tract, with or without associated 2° signs of obstruction. The definitive diagnosis of urinary tract stone was based on documented stone passage or visualization/removal of stone on retrograde studies.

Follow-up: Recruitment over 1y (1 August 1997 to 31 July 1998).

Results

- A total of 62 patients had a urinary tract calculus definitively diagnosed;
- More men with urinary tract calculi than women (51 vs 11), but the age range and mean age were similar;
- A total of 63 patients (54%) had calculi, with or without 2° changes, identified on unenhanced spiral CT;
- Two false-positive results (attributed to phleboliths) and one false-negative result (confirmed by stone passage and retrieval);
- Alternative diagnosis made in seven (6%) patients, including two cases of renal cell carcinoma (RCC), one ureteric transitional cell carcinoma (TCC), and one pelvi-ureteric junction (PUJ) obstruction;
- Other conditions outside the urinary tract were diagnosed in three patients; two had ovarian cysts, and one had sigmoid diverticulitis;
- This series demonstrated a sensitivity of 98% and a specificity of 97% for the detection of calculi.

Discussion

This study is often quoted as reflecting the practicalities of imaging in the UK. The authors concluded that CT allowed rapid, contrast medium-free, anatomically accurate diagnosis of obstructing ureteric stones (with a sensitivity of 98% and a specificity of 97%). They qualified this by stating that there was no information of the degree of obstruction (as there was no visualization of delay in excretion of contrast) and no information on the urothelium (filling defects). The authors did not advocate CT as a replacement for IVU at that time, as, during the study, reporting of CT caused a mean delay of 9h in diagnosis. As urologists have become more familiar with reading CT scans and imaging availability has increased, these concerns have diminished. CT has now replaced IVU as the investigation of choice for ureteric colic.

Renal colic: analgesia

Non-steroidal anti-inflammatory drugs and opioids can significantly relieve the pain in acute renal colic, but opioids (especially pethidine) cause more adverse effects.

AUTHORS: Holdgate A, Pollock T.

REFERENCE: *Cochrane Database Syst Rev* (2004) 1, CD004137.

STUDY DESIGN: Systematic review.

EVIDENCE LEVEL: 1a.

Key message

Patients presenting with renal colic should be prescribed NSAIDs, unless these are contraindicated, in order to relieve pain.

Impact

Before this meta-analysis, both NSAIDs and opioids had been shown to provide pain relief in acute renal/ureteric colic. However, the difference in efficacy between NSAIDs and opioids had not been demonstrated.

Aims

Renal colic has an annual incidence of ~16/10,000 people and a lifetime incidence of 2–5%. The majority of renal calculi will pass spontaneously; therefore, the focus of acute management is rapid pain relief, confirmation of the diagnosis, and recognition of complications requiring immediate intervention. The aim of this review was to examine the benefits and disadvantages of NSAIDs and opioids, and to determine which of these drug types was most appropriate for the management of pain in acute renal colic. In attempting to answer this, all clinically important outcomes (including degree of pain relief, efficacy of pain relief, rate of pain recurrence, and treatment SEs) were explored.

Methods

Studies included: All RCTs or quasi-RCTs comparing any NSAID vs any opioid.

Inclusion criteria:

- All adult patients (age >16y);
- Clinical diagnosis of acute renal colic (pain <12h duration);
- Moderate to severe pain.

Exclusion criteria: Contraindications to either NSAIDs or opiates.

Protocol:

- Studies that reported any one of the following: Patient-rated pain measured by a validated pain scale, time to pain relief, need for rescue medication, rate of pain recurrence, and adverse event rates;
- Review undertaken by two reviewers, who examined the full text of all potentially relevant reviews, to determine which studies satisfied the inclusion criteria;

- RCTs comparing any opioid with any NSAID, regardless of dose or route of administration, were included. A total of 20 trials from nine countries with a total of 1,613 participants were identified.

Results

- Both NSAIDs and opioids lead to clinically significant falls in patient-reported pain scores;
- Ten studies reported lower pain scores in patients receiving NSAIDs;
- Patients treated with NSAIDs were significantly less likely to require rescue medication (RR 0.75, 95% CI 0.61–0.93, $p = 0.007$);
- The majority of trials showed a higher incidence of adverse events in patients treated with opioids;
- There was significantly less vomiting in patients treated with NSAIDs (RR 0.35, 95% CI 0.23–0.53, $p < 0.00001$).

Discussion

The pain of renal colic is due to obstruction of urinary flow, with a subsequent increase in wall tension in the urinary tract. Rising renal pelvic pressure stimulates local synthesis and release of prostaglandins, and subsequent vasodilatation induces a diuresis, which further increases intrarenal pressure. Prostaglandins also act directly on the ureter to induce smooth muscle spasm. Opioids have the advantages of low cost, titratability, and potency. However, there are concerns regarding opiate dependency and drug-seeking behaviour presenting as renal colic. Opioids do not directly act on the cause of pain, which may limit their usefulness. NSAIDs have the theoretical benefit of acting directly on the main cause of pain (prostaglandin release) and have been shown to be effective. However, they are generally not titratable, have a well-recognized SE profile (including renal failure and GI bleeding). Single bolus doses of both NSAIDs and opioids provide pain relief to patients with acute renal colic. However, patients receiving NSAIDs achieve greater reduction in pain scores and are less likely to require further analgesia in the short term. Opioids are associated with a higher rate of vomiting than NSAIDs, and this is particularly true for pethidine. Given these findings, the use of an NSAID, rather than an opioid, is recommended. If opioids are to be used either because of contraindications to NSAIDs or ease of titratability, we recommend that it should not be pethidine, given the high rate of associated vomiting.

Problems

- The trials included in this analysis involved a number of different NSAIDs and opioids. This can be put down to international variations regarding drug choice and route of administration. Due to such heterogeneity, many of the results could not be pooled.

Renal colic: treatment of obstructive pyelonephritis

Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi.

AUTHORS: Pearle M, Pierce HL Miller G *et al.*

REFERENCE: *J Urol* (1998) **160**, 1260–4.

STUDY DESIGN: Case control.

EVIDENCE LEVEL: 3.

Key message

The authors showed that stenting and percutaneous nephrostomy both relieve obstruction and infection, and that neither modality demonstrated superiority in promoting more rapid recovery.

Impact

The decision with regard to the method of drainage may be based on logistical factors and surgeon preference. This is especially important in hospitals where limited availability of interventional radiology services, particularly out of hours, is an issue.

Aims

An infected obstructed system is a urological emergency and must be drained expeditiously after initial resuscitation of the patient and administration of IV antibiotics. This study aimed to compare the efficacy of two established techniques—percutaneous nephrostomy vs retrograde ureteral catheterization—for renal drainage in cases of obstruction and infection associated with ureteral calculi.

Methods

Patients: 42 consecutive patients presenting to a single centre in the USA.

Inclusion criteria:

- Presenting with CT KUB-proven obstructing ureteric calculi;
- Clinical signs of infection (defined as a recorded temperature of $>38^{\circ}\text{C}$ or WCC $>17 \times 10^9/\text{L}$).

Groups:

- Percutaneous nephrostomy;
- Retrograde ureteral catheterization.

Follow up: Duration not stated.

Result

Table 32.3 Summary of results

| Measure | Nephrostomy | Catheterization | p |
|-------------------|------------------------|------------------------|-------|
| Time to treatment | 3.4 (\pm 2.4) h | 4.2 (\pm 3.5) h | <0.05 |
| Length of case | 49.2 (\pm 37.6) min | 32.7 (\pm 20.5) min | <0.05 |
| Fluoroscopy time | 7.7 (\pm 4.8) min | 5.1 (\pm 3.3) min | <0.05 |

- Procedural and fluoroscopy times significantly shorter in retrograde ureteral catheterization group (32.7 and 5.1min, respectively) vs percutaneous nephrostomy (49.2 and 7.7min, respectively);
- One treatment failure in the percutaneous nephrostomy group, successfully salvaged with retrograde ureteral catheterization;
- No significant difference in time to normal temperature between nephrostomy vs catheterization (2.3 vs 2.6d, respectively), time to normal WCC (2 vs 1.7d), and length of stay (4.5 vs 3.2d);
- Cost analysis: Catheterization was $\sim 2\times$ the cost of nephrostomy (see Table 32.3).

Discussion

As mentioned previously, the decision with regard to the method of drainage may be based on logistical factors and surgeon preference. Despite this evidence, the authors concluded that the majority of surgeons would opt for nephrostomy in an infected obstructed system. Concerns over ureteric stent insertion in these patients include potential poor drainage of pus, insertion of a foreign object in the presence of infection, and the potential complications of undergoing general anaesthesia.

Problems

- Sample size was too small for accurate comparison of time to clinical improvement with positive cultures.
- No statistical analysis of cost differences—a full economic evaluation would be helpful in service planning.
- Nodcccsdd

Renal calculi: nephrolithiasis

Lower pole 1: a prospective randomized trial of extracorporeal shock wave lithotripsy and percutaneous nephrolithotomy for lower pole nephrolithiasis—initial results.

AUTHORS: Albala D, Assimos D, Clayman R et al.

REFERENCE: *J Urol* (2001) **166**, 2072–80 (erratum *J Urol* (2002) **167**, 1805).

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Stone clearance from the lower pole following shock wave lithotripsy is poor, especially for stones >10mm in diameter. Calculi >10mm in diameter are better managed initially with percutaneous removal, due to its high degree of efficacy and acceptable low morbidity.

Impact

Extracorporeal shock wave lithotripsy (ESWL) still remains the preferred approach for most patients with lower pole stones ≤1cm, as it is less invasive and does not require general anaesthesia. In addition, patients who fail ESWL should be treated with percutaneous nephrolithotomy (PCNL) or ureterorenoscopy (URS), after an informed discussion with their urologist.

Aims

This prospective randomized, multicentre clinical trial aimed to compare shock wave lithotripsy and percutaneous stone removal for symptomatic lower pole only renal calculi ≤30mm.

Methods

Patients: 128 patients enrolled from multiple centres; 60 randomized.

Inclusion criteria: Symptomatic lower pole only renal calculi ≤30mm.

Groups:

- PCNL ($n = 60$);
- ESWL ($n = 68$).

Primary outcome: Post-operative stone-free rates at 3mo.

Follow up: 3mo.

Results

- Groups: PCNL—58 patients treated, two awaiting treatment, mean stone size 14.43mm; ESWL—64 patients treated, four awaiting treatment, mean stone size 14.03 mm;
- Overall stone-free rates: 95% (PCNL) vs 37% (ESWL) ($p < 0.001$);

- Impact of stone size: Stone clearance from the lower pole from ESWL, stratified by stone size, showed a significant drop when stone was >10mm (63% when ≤10mm, only 23% when >10mm);
- Treatment failure: nine (ESWL) vs none (PCNL);
- Complication rates: 12% and 23% for ESWL and PCNL, respectively;
- Re-treatment: Needed in ten (16%) ESWL and five (9%) PCNL cases;
- Overall morbidity: Low for both 22% (PCNL) and 11% (ESWL) ($p = 0.087$);
- Cost analysis: PCNL and ESWL equally effective in stones <10mm, but PCNL more cost-effective for larger stones.

Discussion

The authors suggest that PCNL should be regarded as the 1° approach for lower pole stones >10mm. However, the role of URS in the management of stones was not considered. This issue was addressed in the subsequent 'Lower pole 2' (Pearle M, Lingeman J, Leveillee R *et al.*, *J Urol* (2005) **173**, 2005–9) and other studies. URS could be considered a less morbid treatment modality for patients with lower pole stones who failed ESWL, as opposed to PCNL. The success rate of URS for lower pole stones is relatively high (86% for stones larger than 20mm). However, the anatomy of the lower pole, much like how it affects ESWL success, can influence the rates of stone clearance in ureteroscopy (i.e. an acute angle may prevent passage of the laser fibre to the stone by limiting flexion of the scope). In contrast to the results for ureteroscopy and ESWL, PCNL outcomes are independent of stone size and intrarenal anatomy.

Problems

- Small sample size (only 60 randomized).
- High loss to F/U (only 88% followed up at 3mo).

Prostate cancer: prevention with finasteride

PCPT (Prostate Cancer Prevention Trial): The influence of finasteride on the development of prostate cancer.

AUTHORS: Thompson I, Goodman P, Tangen C et al.

REFERENCE: *N Engl J Med* (2003) **349**, 215–24.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Long-term therapy with finasteride decreases the incidence of prostate cancer, although there is a small increase in high-risk cancers and sexual SEs.

Impact

The outcomes were greeted with a mixed reception, due to concerns regarding the higher incidence of high-grade tumours with finasteride.

Aims

Most approaches to prostate cancer focus on treatment, rather than prevention. Androgens are known to influence the development of prostate cancer. Finasteride (a 5- α reductase inhibitor) inhibits the conversion of testosterone to dihydrotestosterone, the 1° prostatic androgen. This study aimed to determine whether finasteride could prevent prostate cancer in men aged ≥ 55 y.

Methods

Patients: 18,882 men from 221 centres in the USA; 92% white, 4% African American, 4% other ethnicity.

Inclusion criteria:

- Age ≥ 55 y, no significant co-morbidities or evidence of prostate cancer;
- Normal digital rectal examination (DRE);
- PSA ≤ 3.0 ng/mL;
- AUA symptom score < 20 .

Groups:

- 5mg finasteride ($n = 9,423$);
- Placebo ($n = 9,459$).

Primary endpoint: Development of prostate cancer (histologically proven).

Other factors assessed:

- Changes over time of PSA and prostate volume;
- Effect of finasteride on stage/grade of any developing prostate cancer;
- Accuracy of DRE and PSA in detecting prostate cancer.

Follow-up: Recruitment from 1993 to 1997. Stopped in 2003 (significantly lower incidence of prostate cancer in those taking finasteride). Mean F/U 7y. Annual PSA and DRE measurements. Prostate biopsy if PSA >4ng/L, abnormal DRE, or at end of 7y if no prior abnormality.

Results

Table 32.4 Summary of results

| | Finasteride | Placebo | <i>p</i> |
|--|--|--|--|
| Number randomized | 9,423 | 9,459 | — |
| Number participated | 4,368 | 4,692 | — |
| All tumours detected | 803 (18.4%) | 1,147 (24.4%) | <0.001 |
| % of above tumours (T _{1/2}) | 97.7% | 98.4% | Not stated |
| % of above tumours = high-grade (Gleason 7–10) | 37.0% (280 of 757 graded tumours) or 6.4% of total 4,368 | 22.2% (237 of 1,068 graded tumours) or 5.1% of total 4,692 | <0.001 (comparison of % of all graded tumours) |
| End-of-study biopsies positive for malignancy | 368/3,652 (10%) | 576/3,820 (15%) | <0.001 |

Patient losses between randomization and participation due to early study termination, death, refusal of biopsy, and loss to F/U.

- PSA and cancer detection: 21.1% of the cancer-positive end-of-study biopsies were in patients with PSA 2.5–3.9ng/mL or less; 15.4% of tumours were high-grade in those with PSA ≤2.5ng/mL (see Table 32.4);
- SEs:
 - Sexual SEs (decreased ejaculate volume, ED, loss of libido) significantly commoner in the finasteride group (all *p* ≤0.001);
 - Breast cancer incidence same in both groups (one case, ns).
 - BPH/LUTS commoner in the placebo group (all *p* ≤0.001, except for urinary incontinence).

Discussion

Administration of finasteride resulted in a 24.8% reduction in the prevalence of prostate cancer over the F/U period; however, it was associated with a greater number of sexual SEs and an increased risk of developing higher-grade disease (more likely to undergo clinical progression). This was proposed as being due to lower levels of dihydrotestosterone. Clinically significant tumours were common in patients with both normal and elevated PSA levels.

Problems

- No trial-entry prostate biopsies; these would have been useful, given the high incidence of positive end-of-trial biopsies.
- Higher rates of cancer detection in the placebo group (24.4%) than previously quoted lifetime incidence (16.7%). The authors suggest this was due to overdiagnosis of the disease.

Prostate cancer: hormone and radiotherapy

Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial.

AUTHORS: Bolla M, Collette L, Blank L et al.

REFERENCE: *Lancet* (2002) **360**, 103–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Immediate androgen suppression with a luteinizing hormone-releasing hormone (LHRH) analogue, given during and for 3y after external irradiation, improves DFS and overall survival of patients with locally advanced prostate cancer.

Impact

Use of LHRH analogues has now become standard practice.

Aims

The long-term outcome after external irradiation alone in locally advanced prostate cancer (stage T3–4 N0 M0) is poor. Androgen suppression had been suggested to improve outcomes, possibly by elimination of occult systemic disease, with previous studies having shown an improvement in overall survival. This study aimed to investigate the added value of long-term androgen suppression, in addition to external beam radiotherapy (EBRT), in the treatment of locally advanced prostate cancer.

Methods

Patients: 415 patients across multiple centres worldwide.

Inclusion criteria:

- Age <80y;
- New diagnosis of histologically proven T1–2 prostate adenocarcinoma of grade 3 or stage T3–4 N0–N1 M0 of any grade.

Exclusion criteria:

- Previous history of malignant disease (except adequately treated BCC of the skin);
- Evidence of distal metastasis (including involvement of common iliac or para-aortic lymph nodes).

Groups:

- Combined: 3y of hormone ablation + EBRT ($n = 207$);
- EBRT alone ($n = 208$).

In both groups, 50Gy radiation was delivered to the pelvis over 5wk, and 20Gy over 2wk as a prostatic boost. Goserelin (3.6mg SC every 4wk) was started on the first day of irradiation and continued for 3y. Cyproterone acetate (150mg orally) was given for 1mo, starting 1wk before the first goserelin injection.

Primary endpoint: DFS at 5y. Local failure defined as an increase of >50% of the product of the two maximum perpendicular diameters of the 1° lesion, measured by CT or US.

Secondary endpoints: Acute/late SEs.

Follow-up: PSA and testosterone measured 2mo after end of EBRT, then every 3mo for 3y, and every 6mo thereafter. Median F/U 66mo (range 1–126mo).

Results

- Patients receiving treatment: 196 (EBRT); 195 (combined);
- F/U PSA results available for 388 patients (94%);
- 5y clinical DFS: EBRT alone 40% (95% CI 32–48) vs combined 74% (95% CI 67–81) ($p = 0.0001$);
- 5y overall survival: EBRT alone 62% (52–72) vs combined 78% (72–84) ($p = 0.0002$, HR 0.51, 95% CI 0.36–0.73);
- 5y specific survival: EBRT alone 79% (72–86) vs combined 94% (90–98) ($p = 0.0001$, HR 0.26, 95% CI 0.14–0.44);
- Progression (at median F/U 65.7mo): 90 patients (EBRT alone) vs 27 (combined);
- Death: 78 (EBRT alone) vs 50 (combined).

Discussion

This study demonstrated that an LHRH analogue, given during and for 3y after EBRT, improved both DFS and 5y overall survival in patients with locally advanced prostate cancer, compared with EBRT alone. The adequate duration of androgen deprivation therapy is not yet known. The period of 3y of adjuvant hormonal treatment was chosen empirically, and shortening of this period (as practised in the UK) significantly reduces the cost burden and duration of SEs. In the future, management of locally advanced prostate cancer will likely be tailored according to prognostic factors, with a possible escalation of the dose and the addition of chemotherapy to hormonal treatment for high-risk categories.

Problems

- Poor compliance led to F/U testosterone data only being available for 110 patients (as opposed to 388 patient data for PSA).

Prostate cancer: active surveillance vs radical prostatectomy

Radical prostatectomy versus watchful waiting in early prostate cancer.

AUTHORS: Bill-Axelsson A, Holmberg L, Ruutu M *et al.*

REFERENCE: *N Engl J Med* (2005) **352**, 1977–84.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression.

Impact

Alongside the recent PIVOT (Prostate cancer Intervention Versus Observation Trial) study (*J Natl Cancer Inst Monogr* (2012) **45**, 184–90), this remains one of the few RCTs that have assessed the role of 1° therapy in prostate cancer. Previous attempts by the MRC had to close, due to poor recruitment.

Aims

Prostate cancer is the commonest non-cutaneous malignancy and one of the leading causes of cancer death in men. While radical prostatectomy had become increasingly popular, its efficacy had not previously been quantified. This study aimed to assess the role of 1° treatment in prostate cancer, comparing radical prostatectomy with watchful waiting. The authors had two main hypotheses—firstly, that the relative reduction in the risk of death due to prostate cancer after surgery increases over time, because removal of the 1° tumour prevents metastasis; secondly, that radical prostatectomy significantly improves overall survival.

Methods

Patients: 695 men from 14 centres in Sweden, Finland, and Iceland were enrolled.

Inclusion criteria:

- Age <75y;
- Newly diagnosed, untreated, localized prostate cancer (T2 or less) with well or moderately differentiated tumour;
- Bone scan that showed no abnormalities;
- PSA level of <50ng/mL.

Groups:

- Radical prostatectomy ($n = 348$): Surgery started with dissection of pelvic nodes—if no sign of metastasis from frozen sections, then completed a retropubic radical prostatectomy;
- Watchful waiting ($n = 347$).

Primary endpoint: Death due to prostate cancer.

Secondary endpoints: Death from any cause, metastasis, and disease progression.

Follow up: Every 6mo for first 2y, then annually for a clinical examination and blood tests (Hb, PSA, ALP, and creatinine levels). Bone scan and chest radiograph taken annually (until 1997), then annually for first 2y only. Mean F/U 8.2y.

Results

- A total of 12% had T1c tumours (non-palpable, PSA detected); 76% had T2 tumours;
- Deaths due to prostate cancer: Significantly fewer in the prostatectomy vs waiting group (30 vs 50, $p = 0.01$);
- Overall deaths: Fewer in the prostatectomy vs waiting group (106 vs 83, $p = 0.04$);
- Reduction in risk of death: Radical prostatectomy provided a 44% RRR in prostate cancer death at 10y, and an improvement in disease-specific and overall survival at 10y;
- Distant metastasis: Similar in first 5y (8.1% prostatectomy vs 9.8% waiting, $p = 0.42$), but 10.2% lower with prostatectomy vs waiting (RR 0.6, 95% CI 0.42–0.86) at 10y.

Discussion

When radical prostatectomy was compared with watchful waiting for patients with prostate cancer, the 10y absolute differences in disease-specific and overall mortality were statistically significant by 5.3% ($p = 0.01$) and 5.0% ($p = 0.04$), respectively, favouring radical prostatectomy. Prostatectomy also offered a lower cumulative incidence of distant metastasis at 10y. The authors expect that the benefits of surgery would increase during longer periods of F/U.

Problems

- A total of 75% of the cases were T2 tumours, which is in contrast to present-day practice where only 15% of cases are T2 tumours.
- The cancer-specific survival was only improved in men <65y of age.

Bladder cancer: assessment of haematuria

A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice.

AUTHORS: Khadra M, Pickard R, Charlton M et al.

REFERENCE: *J Urol* (2000) **163**, 524–7.

STUDY DESIGN: Cohort.

EVIDENCE LEVEL: 2b.

Key message

In the assessment of haematuria, cystoscopy cannot be safely avoided, even in younger patients with only microscopic haematuria. In this study, only a combination of US and intravenous pyelogram (IVP) detected all upper tract tumours.

Impact

Along with the conclusions of Edwards et al. (*BJU Int* (2006) **97**, 301–5), this paper provides the evidence base for the investigation of haematuria, informing the Joint Consensus Statement on the Initial Assessment of Haematuria (2008). From a referral perspective, this established clear guidelines for referral to an urologist. All cases of visible haematuria, all cases of symptomatic non-visible haematuria, and all cases of non-visible haematuria occurring in the over 40s should be referred to a urologist for urgent assessment.

Aims

The commonly accepted pathway for investigating haematuria had included excretory urography (IVP) and cystoscopy. Some had suggested that US of the upper urinary tract was adequate and that cystoscopy was not necessary in younger patients with microscopic haematuria. This study sought to ascertain whether a less intensive algorithm for the assessment of haematuria could be adopted, while retaining diagnostic efficacy.

Methods

Patients: 1,930 patients attending a single haematuria clinic.

Inclusion criteria: All patients aged >40y with visible or non-visible haematuria.

Protocol: All patients underwent a history and examination, routine blood tests, urinalysis, cytology, plain abdominal radiography, renal US, IVU, and flexible cystoscopy.

Results

- A total of 1,194 ♂ and 736 ♀, with a mean age of 58y (range 17–96), were included;
- A total of 61% of patients had no pathology identified; 12% were diagnosed with bladder cancer; 13% had UTI, and 2% had stone disease;
- Macroscopic and microscopic haematuria resulted in cancer diagnosis in 24% and 9.4% of patients, respectively;
- Bladder cancer was found in more patients with microscopic haematuria than the ≤5% reported within previous urological literature.

Discussion

The key finding of this paper is that, if only US or IVU had been performed, four cases of upper tract malignancy would have been missed. Therefore, the use of both imaging modalities is recommended. Normal findings from both of these investigations suggest a low possibility of any serious urological tract pathology being missed; however, patients may still require further investigation (e.g. for proteinuria) from renal physicians to determine alternative renal causes of their haematuria. Note that, in current practice, excretory urography, in the form of a CT urogram, is more commonly used, especially in those for whom one has a high index of clinical suspicion for cancer.

Bladder cancer: post-operative intravesical therapy

A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials.

AUTHORS: Sylvester R, Oosterlinck W, van der Meijden A *et al.*

REFERENCE: *J Urol* (2004) **171**, 2186–90.

STUDY DESIGN: Meta-analysis.

EVIDENCE LEVEL: 1a.

Key message

One immediate intravesical instillation of mitomycin C (MMC) chemotherapy significantly decreases the risk of recurrence after transurethral resection of bladder tumour (TURBT) in patients with stage Ta/T1 single and multiple bladder cancer. It is the treatment of choice in patients with a single low-risk papillary tumour and is recommended as the initial treatment after transurethral resection (TUR) in patients with higher-risk tumours.

Impact

This meta-analysis is one of three meta-analyses published by Sylvester *et al.*, advocating the use adjuvant intravesical treatment following TURBT, and supports earlier research (e.g. Tolley *et al. BMJ* (1988) **296**, 1759–61). The use of MMC is now the standard of care post-TURBT.

Aims

In patients with Ta or T1 tumours who were followed for a minimum of 20y or until death, the risk of bladder cancer recurrence after initial resection was 80%. Adjuvant chemotherapeutic agents had therefore been proposed to reduce this risk. This meta-analysis reviewed the existing evidence base to determine if one single immediate instillation of intravesical chemotherapy after TUR decreased the risk of recurrence in patients with stage Ta/T1 single and multiple bladder cancer, both overall and separately.

Methods

Inclusion criteria:

- RCTs comparing TUR alone to TUR plus one immediate instillation of chemotherapy;
- Patients with stage Ta or T1 bladder cancer;
- Agents studied included epirubicin, MMC, thiotepa, and pirarubicin.

Exclusion criteria: Studies including patients in whom there was either excessive bleeding or concomitant urethral or prostate cancer.

Results

- A total of 7 RCTs with recurrence information on 1,476 patients, with median F/U of 3.4y (max 14.5y);
- A total of 267/728 patients (36.7%) receiving one post-operative instillation of intravesical chemotherapy had recurrence, compared with 362/748 patients (48.4%) who had recurrence with TUR alone (OR 0.61, $p < 0.0001$);
- Intravesical chemotherapy conferred a 39% decrease in the relative risk of recurrence;
- There was a clear benefit in patients with a single tumour (849 patients from four studies, OR 0.61, $p = 0.0005$) and, to a lesser extent, in those with multiple tumours (111 patients from two studies, OR 0.44, $p = 0.06$);
- However, after one instillation, 65.2% of patients with multiple tumours had recurrence, compared to 35.8% of patients with single tumours, showing that one instillation alone is insufficient treatment for patients with multiple tumours.

Discussion

Although a single instillation is the standard of care after TURBT, a 6-dose (weekly) course of MMC may be necessary. In addition, it is important to note that MMC does not prevent progression of recurrent TCC. In high-risk cases, bacille Calmette–Guérin (BCG) is optimal. As a result of this and other papers, the European Association of Urology (EAU) guidelines on non-muscle-invasive bladder TCC and, to a lesser extent, the AUA guidelines recommended that an immediate instillation of chemotherapy be given after TURBT, except in patients with an extended TURBT (risk of perforation and extravasation of the drug). Subsequent studies have not contradicted these conclusions, with two supporting these findings (Berrum-Svennung *et al.*; Gudjonsson *et al.*) and one being equivocal (Cai *et al.*), although the latter was underpowered.

Problems

- The authors themselves questioned the benefit of immediate instillation, on the grounds that this: (a) only prevented small tumour recurrences (half of which would be relatively easily removed with a simple procedure), (b) was not cost-effective (NNT 8.5 with instillation to prevent one TURBT), and (c) was not useful in higher-risk patients.
- A well-powered phase 3 RCT is still needed to definitively confirm/refute the findings supporting the use of MMC.

Further reading

Berrum-Svennung I *et al.* *J Urol* (2008) **179**, 101–6.

Cai *et al.* *J Urol* (2008) **180**, 110–15.

Gudjonsson S *et al.* *Eur Urol* (2009) **55**, 777–80.

Vascular surgery

Introduction 898

Carotid artery stenosis: asymptomatic endarterectomy 900

Carotid artery stenosis: symptomatic endarterectomy 902

Carotid artery stenosis: general anaesthetic vs local
anaesthetic 904

Carotid artery stenosis: stenting vs endarterectomy (1) 906

Carotid artery stenosis: stenting vs endarterectomy (2) 908

Abdominal aortic aneurysm: screening 910

Abdominal aortic aneurysm: small aortic aneurysms 912

Abdominal aortic aneurysm: endovascular vs open repair in 'fit'
patients 914

Peripheral arterial disease: surgery vs angioplasty 916

Peripheral arterial disease: angioplasty vs stenting 918

Varicose veins: surgical technique 920

Venous ulcers: surgery vs compression 922

Introduction

Over the last three decades, vascular surgery has transformed into a new specialty incorporating endovascular therapies. The field of vascular and endovascular therapy covers an extensive range of conditions and disorders of the arteries and veins.

Lower limb ischaemia

Bypass surgery for lower limb ischaemia owes much of its success to the pioneering work of Alexis Carrel in 1902, who described a reliable technique for vascular anastomosis. It was over 60y later when an endovascular alternative, percutaneous transluminal angioplasty, was described by Dotter and Judkins. It was not until 1971 when the pioneering work of Gruntzig led to the introduction of balloon angioplasty in the treatment of arterial stenoses and occlusions. The advent of BMS and DES has created further therapeutic options.

Abdominal aortic aneurysm

Conventional repair of AAA remains largely similar to the technique described by Dubost in 1951. However, outcomes have improved through better understanding and management of their perioperative, anaesthetic, intensive care, and transfusion requirements. In 1991, Volodos and Parodi described a novel, less invasive technique for repairing AAAs by placing a stent graft from within the vessel. Since then, endovascular aneurysm repair (EVAR) has progressed enormously from the initial custom-built devices—with design faults that led to late device failures—to the modular ‘off the shelf’ variety, which have proved more durable.

Carotid disease

Eastcott *et al.* first described carotid endarterectomy (CEA) in 1954, and it was not long before it was considered the standard of care for those patients with carotid artery disease. Carotid revascularization with balloon angioplasty began in the early 1980s, and a stent was first used in 1989 to treat an intimal flap after angioplasty. Since the initial deployment of the first carotid stent in 1989, technological advances have improved the durability and safety of this device and technique.

Varicose veins

The treatment of varicose veins has also seen major developments—traditional thought advocated surgical ligation and ‘stripping’ of incompetent truncal veins. However, minimally invasive techniques, such as endovenous laser ablation and radiofrequency ablation (RFA), have been introduced widely as first-line therapy.

Carotid artery stenosis: asymptomatic endarterectomy

ACST-1 (Asymptomatic Carotid Surgery Trial): Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms.

AUTHORS: Halliday A, Harrison E, Hayter E *et al.*

REFERENCE: *Lancet* (2010) **376**, 1074–84.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Younger patients <75y of age with asymptomatic carotid stenosis of >70% benefit from a 4.9% long-term (10y) reduction in the risk of stroke following CEA, provided that the perioperative stroke and mortality rate is <3.0%.

Impact

The number of CEAs performed in Europe for asymptomatic stenosis has increased by 100% in Scandinavia and the UK, and 25% in mainland Europe. Younger patients (<75y) with asymptomatic significant stenosis (>70%) may be considered for CEA.

Aims

Asymptomatic carotid stenoses are common and usually present a small risk of future stroke. The benefit of CEA in this group of patients was previously unclear. This study aimed to determine the balance of surgical risks and long-term benefits following CEA in patients with significant carotid artery, but no recent neurological symptoms.

Methods

Patients: 3,120 patients from 126 centres in 30 countries (mainly Europe).

Inclusion criteria:

- Severe unilateral or bilateral carotid stenoses (>60% on US);
- No neurological symptoms for the previous 6mo.

Exclusion criteria:

- Previous ipsilateral CEA;
- Poor surgical risk, especially significant CAD;
- Poor life expectancy which precluded long-term F/U;
- Potential cardiac source of emboli.

Groups:

- Surgical 'immediate' CEA and best medical treatment ($n = 1,560$);
- Medical: best medical treatment (unless symptomatic in the F/U period, at which point underwent 'deferred' CEA) ($n = 1,560$).

Primary endpoints:

- Any perioperative mortality, non-fatal stroke, or MI;
- Any non-perioperative stroke.

Follow-up: At 4 and 12mo, and yearly thereafter till death or at least 3y (98% complete; median F/U 9y in survivors).

Results**Table 33.1** Summary of results

| | Surgical (%) | | Medical (%) | | Net gain (%) | | <i>p</i> |
|--|--------------|------|-------------|-------|--------------|-----|----------|
| | 5y | 10y | 5y | 10y | 5y | 10y | |
| Any stroke | 6.9 | 13.4 | 10.9 | 17.9% | 4.1 | 4.6 | <0.0001 |
| Fatal or disabling stroke | 3.5 | — | 6.1% | — | 2.5 | — | <0.004 |
| Any non-perioperative stroke | 41. | 10.8 | 10.0 | 16.9 | 5.9 | 6.1 | <0.0001 |
| Non-perioperative carotid territory ischaemic stroke | 2.7% | — | 9.5 | — | 6.8 | — | <0.0001 |

Kaplan–Meier life table methods to assess 5 and 10y stroke risk—indicates 10y data unavailable.

- 30d perioperative stroke and mortality rate 3.1%;
- Subgroup analysis found no significant heterogeneity in perioperative hazards by age, sex, and extent of stenosis (only 60 such events);
- Men show greater benefit than women within 5y after CEA; similar outcomes by 10y. No significant benefit found for older patients (>75y) (see Table 33.1).

Discussion

One in eight patients with asymptomatic severe carotid artery stenosis (>70% on US) would have a stroke within 5y. This risk can be halved (one in 16) with CEA. The 10y F/U results indicate that the early benefits of surgery over best medical therapy are maintained over time.

Problems

- While there was an RRR of 50% in favour of surgery, this correlated to an ARR of only 1% per year.
- Maximal benefits of CEA are in younger patients, with life expectancy $\geq 5y$.
- Benefit of surgery only if the perioperative stroke rate is <3%.

Further reading

Chambers B, Donnan G (2005). *Cochrane Database Syst Rev* 4, CD001923.

Carotid artery stenosis: symptomatic endarterectomy

NASCET (North American Symptomatic Carotid Endarterectomy Trial):

Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis.

AUTHORS: NASCET collaborators

REFERENCE: *N Engl J Med* (1991) 325, 445–53.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

CEA reduces the incidence of strokes in patients with symptomatic ipsilateral high-grade stenosis (70–99%) of the ICA.

Impact

CEA has become an integral part of stroke prevention and should be considered for every patient following a recent TIA or non-disabling ischaemic stroke with an ipsilateral significant carotid stenosis of >70%.

Aims

Despite the lack of good evidence of benefit, the number of CEAs performed in the USA for stroke prevention increased dramatically until the mid 1980s, then declined. This study aimed to correlate the relationship between the degree of carotid stenosis with outcome from treatment.

Methods

Patients: 659 patients from 50 clinical centres in the USA and Canada.

Inclusion criteria:

- Hemispheric or retinal TIA, or non-disabling stroke within 120d;
- 70–99% stenosis in the symptomatic ICA measured by 2-planar selective angiography.

Exclusion criteria:

- Severe intracranial atherosclerotic stenosis;
- Organ failure or cancer with poor life expectancy;
- Disabling stroke;
- Cardiac valvular or rhythm disorder likely to cause embolic symptoms;
- Uncontrolled HTN, unstable angina, recent (6mo) MI, or recent major surgery (previous 30d).

Groups:

- Medical treatment: aspirin plus a combination of antilipid, antihypertensive, and antidiabetic therapy, as indicated ($n = 331$);
- Surgical treatment: CEA plus best medical treatment ($n = 328$).

Primary endpoints:

- Fatal and non-fatal ipsilateral stroke;
- Any stroke or death.

Follow-up: At 1, 3, 6, 9, and 12mo, then every 4mo by neurologists. CT brain and carotid duplex performed for every new suspected cerebrovascular event.

Results

Table 33.2 Summary of results

| Adverse events at 2y F/U* | Medical patients | Surgical patients | Absolute difference | Relative risk reduction |
|-----------------------------------|------------------|-------------------|---------------------|-------------------------|
| Ipsilateral stroke | 61 (26.0%) | 26 (9.0%) | 17.0 ± 3.5% | 65% |
| Major or fatal ipsilateral stroke | 29 (13.1%) | 8 (2.5%) | 10.6 ± 2.6% | 81% |
| Any stroke or death | 73 (32.3%) | 41 (15.8%) | 16.5 ± 4.2% | 51% |

* Kaplan–Meier estimates.

- Perioperative stroke and death rate was 5.8%, reduced to only 2.1% if only major strokes were considered;
- Safety Monitoring Board prematurely stopped the enrolment of patients with 70–99% stenoses and issued a ‘clinical alert’ informing physicians of the results. Patients in the medical arm with high-grade stenoses were subsequently offered surgery. (See Table 33.2.)

Discussion

Among symptomatic patients with high-grade stenosis (70–99%), those who underwent surgery benefited from an ARR of 17% in the risk of ipsilateral stroke at 2y, representing a 65% RRR. Although this study is nearly 20y old, it remains a seminal source of evidence to justify CEA for symptomatic carotid plaques.

Problems

- Surgical results of the vascular surgeons or neurosurgeons in NASCET were reviewed by the surgical committee, before each centre was certified, and morbidity and mortality rates had to be ≤5%.
- While inclusion criteria were based on angiography, NASCET’s angiography/US findings were subject to ~15% error.
- Carotid stenoses are currently measured with duplex US, not angiography.

Further reading

Rerkasem K, Rothwell PM (2011). *Cochrane Database Syst Rev* 4, CD001081.

Carotid artery stenosis: general anaesthetic vs local anaesthetic

GALA (General Anaesthesia vs Local Anaesthesia for carotid surgery):

Comparison of outcomes for carotid endarterectomy under general anaesthesia Vs carotid endarterectomy under local anaesthesia.

AUTHORS: GALA Trial Collaborative Group.

REFERENCE: *Lancet* (2008) **372**, 2132–42.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

No difference in post-operative stroke, MI, death, length of hospital stay, or QoL between patients undergoing CEA under general (GA) or local anaesthesia (LA).

Impact

Either GA or LA may be used, depending on operative team experience and patient circumstances.

Aims

The benefit of CEA in lowering the risk of stroke from carotid disease needs to be balanced by complications during or soon after surgery. CEA may be performed under GA or LA, with the latter hypothesized to reduce perioperative risk through less frequent shunt use, fewer cardiorespiratory complications, and preserved cerebrovascular autoregulation. This study compared the outcome of CEA performed under GA with that under LA.

Methods

Patients: 3,526 patients from 95 centres in 24 countries.

Inclusion criteria:

- Patients with symptomatic or asymptomatic internal carotid stenosis for whom CEA with either LA or GA was advised.

Exclusion criteria:

- Simultaneous bilateral CEA;
- CEA combined with another operative procedure;
- Patients who had previously taken part in the trial.

Groups:

- GA group ($n = 1,752$);
- LA group ($n = 1,771$).

Primary endpoint:

- Proportion of patients with stroke, MI, or death between randomization and 30d after anaesthesia.

Secondary endpoints:

- Survival free of stroke, MI, or death up to 1y after anaesthesia;
- Length of stay in recovery, HDUs, ICUs, and overall in hospital;
- HRQOL.

Follow-up: 7d, 1mo, and 1y post-procedure.

Results

- Median time from randomization to surgery was 1d in both groups;
- Lengths of stay in GA and LA groups were not significantly different;
- The proportion of operations performed by trainee surgeons and anaesthetists was the same in both groups;
- One in five patients were not on antithrombotic medication pre-randomization. (See Table 33.3.)

Table 33.3 Summary of results

| Outcomes between randomization and 30d after anaesthesia | GA | LA |
|--|------|------|
| Stroke | 4.0% | 3.7% |
| MI | 0.2% | 0.5% |
| Death (any cause) | 1.5% | 1.1% |
| Primary outcome | 4.8% | 4.5% |

Discussion

In terms of the primary endpoints of MI, stroke, and death, there is no reason to favour GA over LA or vice versa for CEA. Similarly, the type of anaesthetic has no influence over the length of stay or QoL. Ideally, surgical and anaesthetic teams should be competent at both techniques to meet the needs of a heterogeneous patient population.

Problems

- The study did not reach the planned sample size of 5,000 patients, possibly because surgeons and anaesthetists avoided randomizing high-risk patients who they deemed unsuitable for one type of anaesthetic or the other.
- Absence of blinding may have caused bias in recognition or assessment of outcomes.
- Preoperative statin usage not recorded.

Carotid artery stenosis: stenting vs endarterectomy (1)

CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial): Endarterectomy versus stenting in symptomatic and asymptomatic patients with high-grade carotid stenosis.

AUTHORS: Mantese VA, Timaran CH, Chiu D et al.

REFERENCE: *Stroke* (2010) **41**, S31–S34.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Carotid artery stenting (CAS) and CEA had similar medium-term (4y) outcomes of death, MI, and stroke. Periprocedure, there was a higher risk of stroke (with CAS) or MI (CEA).

Impact

CEA and CAS may both be performed safely by experienced operators. This study supports the continued use of CEA as gold standard therapy for stroke reduction from carotid plaques, while highlighting the reduced cardiac risk associated with CAS.

Aims

CAS provides a minimally invasive approach for the treatment of carotid stenosis. However, CEA is associated with good outcomes and a low risk of major stroke or death. This study aimed to determine whether CAS was a viable alternative to CEA in symptomatic and asymptomatic patients with significant (70–99%) carotid artery stenosis, as previous evidence had conflicting outcomes.

Methods

Patients: 2,502 patients from 117 approved clinical centres in the USA (operators at each site were selected through a stringent validated selection process (CEA) or training and credentialing programme (CAS)).

Inclusion criteria:

- Symptomatic patients:
 - TIA, amaurosis fugax, or non-disabling stroke in the distribution of the studied artery within 180d of randomization;
 - Stenosis >70% (US) or >50% (angiography);
- Asymptomatic patients:
 - Stenosis >70% (US) or >60% (angiography).

Exclusion criteria:

- Previous disabling stroke;
- Chronic AF.

Groups:

- CAS: RX Acculink stent + RX Accunet embolic protection device. Antiplatelet therapy given pre- and post-procedure ($n = 1,262$);
- CEA: Standard CEA as per surgeons' preferences. Antiplatelet therapy given pre- and post-procedure ($n = 1,240$).

Primary endpoint:

- Occurrence of any stroke, MI, or death in F/U period.

Follow-up: Carotid US, modified Rankin scale, and NIHSS at 1, 6, and 12mo, and then annually until 4y post-procedure. Phone interview every 6mo.

Results**Table 33.4** Summary of results

| | CAS* No. of patients (% \pm SE) | CEA* No. of patients (% \pm SE) | Absolute treatment effect of CAS vs CEA (95% CI)* | <i>p</i> |
|--------------------------|---|---|---|----------|
| Any stroke | 105 (10.2 \pm 1.1) | 75 (7.9 \pm 1.0) | 2.3 (−0.6 to 5.2) | 0.03 |
| Major ipsilateral stroke | 16 (1.4 \pm 0.3) | 6 (0.5 \pm 0.2) | 0.8 (0.1 to 1.6) | 0.05 |
| Minor ipsilateral stroke | 52 (4.5 \pm 0.6) | 36 (3.5 \pm 0.6) | 1.0 (−0.7 to 2.7) | 0.10 |
| Primary endpoint | 85 (7.2 \pm 0.8) | 76 (6.8 \pm 0.8) | 0.4 (−1.7 to 2.6) | 0.51 |

* 4y study period, including 30d periprocedural period.

- Similar periprocedural incidence of the primary endpoint in both groups. However, components were different: stroke commoner with CAS (4.1% vs 2.3%; $p = 0.012$), and MI commoner with CEA (2.3% vs 1.1%; $p = 0.032$);
- After the 30d periprocedural period, the ipsilateral stroke risk was low and similar in both groups (CAS 2.4% vs CEA 2.0%);
- Neither symptomatic status nor sex affected treatment difference;
- Outcomes better for CAS (<70y) and after CEA (>70y). (See Table 33.4.)

Discussion

Symptomatic and asymptomatic patients with high-grade stenoses treated with CAS had similar medium-term outcomes to those treated with CEA. CAS had better outcomes in younger patients (<70y), but with higher rates of periprocedural stroke. CEA had better outcomes in older patients (>70y), but with higher rates of periprocedural MI.

Problems

- Only one stent system was used, though several are available.
- No medical arm was included in the study.

Further reading

Bonati LH, et al. (2012). *Cochrane Database Syst Rev* 9, CD000515.

Carotid artery stenosis: stenting vs endarterectomy (2)

EVA-3S (Endarterectomy Vs Angioplasty in patients with Symptomatic Severe carotid Stenosis): Endarterectomy vs stenting in patients with symptomatic severe carotid stenosis.

AUTHORS: Mas JL, Trinquart L, Leys D et al.

REFERENCE: *Lancet Neurol* (2008) 7, 885–92.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Among patients with symptomatic carotid stenosis of >60%, CEA is safer than CAS.

Impact

CEA remains the gold standard treatment for symptomatic stenosis.

Aims

This study aimed to determine whether outcomes after CAS were comparable to CEA in patients with symptomatic critical ICA stenosis.

Methods

Patients: 527 patients from 30 vascular centres in France (operators performed >25 CEA or >12 CAS in the preceding year, before being approved. Criteria less strict than in CREST study).

Inclusion criteria:

- TIA or non-disabling stroke within 120d of enrolment in the trial;
- Stenosis of 60–99% in the symptomatic ICA, confirmed by catheter angiography or magnetic resonance angiography (MRA).

Exclusion criteria:

- Disabling stroke (≥ 3 on Rankin score);
- Severe tandem lesions (proximal common carotid, intracranial);
- Previous ipsilateral carotid surgery;
- Non-atherosclerotic carotid disease;
- Bleeding disorders or contraindications to heparin, ticlopidine, or clopidogrel;
- Uncontrolled HTN or DM, unstable angina, and other co-morbidities leading to life expectancy of <2y.

Groups: Treatment within 2 wk of randomization.

- CEA ($n = 262$);
- CAS ($n = 265$): Included embolization protection devices. Had aspirin plus clopidogrel or ticlopidine for 3d before, and 30d after, stenting.

Primary endpoint: 30d incidence of any death or stroke.

Secondary endpoints:

- Composite of any stroke or death from treatment to end of F/U;
- MI, TIA, local complications, cranial nerve injury.

Follow-up: Neurologist review at 48h, 30d, 6mo, and every 6mo thereafter until 4y post-procedure.

Results

- One additional stroke or death resulted when 17 patients underwent CAS, rather than CEA (absolute risk increase of 5.7%);
- Excess risk associated with CAS was greater in men and in patients >70y of age. (See Table 33.5.)

Table 33.5 Summary of results

| | CEA | CAS | RR or HR | p |
|--|-------|-------|----------|------|
| 30d incidence of stroke or death | 3.9% | 9.6% | RR 2.5 | 0.01 |
| 4y incidence of stroke or death | 21.6% | 26.9% | HR 1.39 | 0.08 |
| 30d incidence of disabling stroke or death | 1.5% | 3.4% | RR 2.2 | 0.3 |
| 4y incidence of disabling stroke or death | 17.0% | 19.6% | HR 1.20 | 0.41 |
| 4y risk of non-procedural stroke (31d–4y) | 4.94% | 4.49% | HR 1.02 | – |
| 4y risk of non-procedural death | 16.0% | 16.1% | HR 1.07 | – |

Kaplan–Meier life table methods to assess the 4y stroke risk.

Discussion

Trial stopped early for safety and futility. The risk of perioperative stroke or death was significantly higher after CAS than CEA. This was largely accounted for by the higher 30d periprocedural risk with CAS. Beyond this period, the risk of stroke was low and similar in both groups.

Problems

- The incidence of stroke after stenting was 9.2%. This was significantly higher than previously reported in other studies or stent registries.
- Different stents and cerebral protection devices were used.
- No specified antiplatelet regime for patients having CEA.

Further reading

Bonati L, et al. (2012). *Cochrane Database Syst Rev* 9, CD000515.

Abdominal aortic aneurysm: screening

MASS (Multicentre Aneurysm Screening Study): Effect of abdominal aortic aneurysm screening on mortality in men.

AUTHORS: Multicentre Aneurysm Screening Study Group.

REFERENCE: *Lancet* (2002) **360**, 1531–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Population screening for AAA in men aged 65–74y significantly reduces AAA-related deaths.

Impact

In the UK, phased implementation of the National Abdominal Aortic Aneurysm Screening Programme began in 2009.

Aims

Ruptured AAA is responsible for 2–3% of all deaths in men older than 65y. This study aimed to assess whether US screening for AAAs was beneficial, in terms of mortality, morbidity, and QoL.

Methods

Patients: 67,800 men from four centres (Oxford, Winchester, Southampton, and Portsmouth) in the UK.

Inclusion criteria:

- ♂ aged 65–74y;
- Resident in any trial centre area.

Exclusion criteria:

- Critical illness or serious health problems preventing screening test;
- Previous aortic surgery.

Groups:

- Invited: Invited for an abdominal US scan ($n = 33,839$);
- Control: Not invited ($n = 33,961$).

Primary endpoint: Aneurysm-related mortality.

Secondary endpoints:

- All-cause mortality;
- Frequency of ruptured AAA;
- QoL.

Follow-up: Mean F/U 4.1y:

- <5.5cm aneurysm: Received surveillance scans;
- Rapidly expanding, symptomatic, or ≥ 5.5 cm: Referred to a vascular surgeon and considered for surgery.

Results

Table 33.6 Summary of results

| | Control (<i>n</i> = 33,961) | Invited (<i>n</i> = 33,839) | HR | <i>p</i> |
|--------------------------------|---------------------------------|---------------------------------|------|----------|
| Total AAA-related deaths | 113 (0.3%) | 65 (0.2%) | 0.58 | 0.0002 |
| Ruptured AAA | 140 (0.4%) | 82 (0.2%) | 0.59 | 0.00006 |
| Elective AAA repair mortality | 9 (10%) | 15 (5%) | — | 0.1 |
| Emergency AAA repair mortality | 22 (41%) | 8 (30%) | | 0.3 |

- A total of 80% of 'Invited for screening' population accepted and were scanned;
- Aneurysm detected in 4.9% of the men scanned;
- The screened aneurysms were distributed as follows:
 - 3.0–4.4cm AAA: 71%;
 - 4.5–5.4cm AAA: 17%;
 - >5.5cm AAA: 12%.
- RRR of 42% in the invited group and 53% in those who attended the US scan;
- More individuals in the invited group (*n* = 322, 1%) had operations than in the control group (*n* = 92, 0.3%);
- There were fewer emergency operations done in the invited group (*n* = 27, 0.08%) than in the control group (*n* = 54, 0.1%);
- 30d mortality was 6% for elective repair and 37% for emergency operations; no significant differences between the two groups;
- No difference in all-cause mortality between groups (11% died in each group by the end of the trial). (See Table 33.6.)

Discussion

Screening significantly reduced mortality associated with AAA. There was no significant reduction in all-cause mortality between the two groups. This was expected, as AAA only accounted for 2–3% of all deaths. There was good acceptance in USS screening.

Problems

- Mortality data based on death certification by the Office of National Statistics. Many patients are certified without post-mortem, hence the accuracy of the data is uncertain. Coding used to establish AAA-related deaths could have included ruptured thoracic aortic aneurysms.
- Many of the deaths in the invited group were in patients who failed to attend their screening US, did not comply with a subsequent surveillance programme, or were deemed unfit for surgery.
- The incidence of ruptured AAA in the invited group who did not attend reduces the benefit for screening overall.

Further reading

Cosford P, Leng GC (2007). *Cochrane Database Syst Rev* 2, CD002945.

Abdominal aortic aneurysm: small aortic aneurysms

UKSAT (UK Small Aneurysm Trial): Long-term outcomes of immediate repair compared with surveillance of small abdominal aortic aneurysms.

AUTHORS: UK Small Aneurysm Trial Participants.

REFERENCE: *Br J Surg* (2007) **94**, 702–8.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

There is no survival benefit associated with elective open repair of AAAs <5.5cm.

Impact

Elective repair is considered for patients with AAAs >5.5cm in diameter.

Aims

AAAs are common, with a prevalence of around 6% in 65-year-old ♀. Ruptured AAA is associated with high mortality. However, more patients die from other conditions with their aneurysm intact. This study aimed to determine whether early open repair of small AAAs (≤ 5.5 cm in maximum diameter) was beneficial or whether a policy of active surveillance was acceptable.

Methods

Patients: 1,090 patients from 93 centres in the UK.

Inclusion criteria:

- Aged 60–76y;
- Asymptomatic infrarenal AAA of 4.0–5.5cm in diameter;
- Fit for open AAA repair.

Groups:

- Surgical arm: Early elective aneurysm repair ($n = 563$);
- Surveillance arm: Remained on US surveillance and had surgical repair if the aneurysm became symptomatic or expanded by >1 cm/y or exceeded 5.5cm ($n = 527$).

Primary endpoint: All-cause mortality.

Secondary endpoints:

- Aneurysm-related mortality;
- 30d mortality.

Follow-up: This is a 12y F/U report.

Results

Table 33.7 Summary of results

| | Surveillance (n = 527) | Surgery (n = 563) | HR | p |
|---|--|--|------|-------|
| All-cause mortality | 352 (8.8 deaths/ 100 patient years) | 362 (8.0 deaths/ 100 patient years) | 0.90 | 0.139 |
| 30d mortality | 28/389 (7.2%) | 29/526 (5.5%) | – | 0.3 |
| Difference in mean years of survival | 0.33 | | – | 0.184 |

- By the end of the study, 401 (76%) patients in the surveillance group had undergone AAA repair (468 open elective, six emergency open, 26 elective endovascular, and one laparoscopic);
- In the surgical group, 528 (94%) patients had open AAA repair (522 elective open, three emergency open, two elective endovascular, one laparoscopic);
- Mortality for elective AAA repair was 5.0% in the early surgery group and 6.3 % in the surveillance group;
- Estimated cost of treatment was 17% higher (£1,326) in the early surgery group. (See Table 33.7.)

Discussion

Early repair of small AAA did not result in a long-term survival benefit over active surveillance. By the end of the trial, three-quarters of patients in the surveillance group eventually underwent AAA repair. Furthermore, there is a significant cost benefit incurred by the use of active surveillance over early intervention.

Problems

- The study was not designed to specify the size at which AAA should be treated. It used a threshold of 5.5cm for both men and women; 17% of patients in this trial were women, for whom this threshold may have been too high.
- Subgroup analysis demonstrated a benefit for early surgery in younger patients (<72y) with larger AAA (>4.5cm). However, as this study was not powered to assess this group, it does not influence current practice for the majority of clinicians.

Further reading

Filardo G, et al. (2012). *Cochrane Database Syst Rev* 3, CD001835.

Abdominal aortic aneurysm: endovascular vs open repair in 'fit' patients

EVAR-1 (EndoVascular Aneurysm Repair): EVAR vs open repair in patients with abdominal aortic aneurysm.

AUTHORS: The United Kingdom EVAR Trial Investigators.

REFERENCE: *N Engl J Med* (2010) **362**, 1863–71.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

EVAR of AAA is associated with significantly lower operative mortality than open surgical repair. However, no differences were seen in total or aneurysm-related mortality in the long term. EVAR was associated with increased graft-related complications and re-interventions, and was more costly.

Impact

EVAR may be considered as a treatment option for patients with AAA, in whom open surgical repair would also be appropriate. The role of EVAR in patients considered low-risk for open surgical repair and with longer life expectancy remains an area of debate.

Aims

While short-term data had suggested EVAR to reduce morbidity and mortality, compared to conventional surgery, its durability had remained a concern. This study aimed to compare clinical effectiveness and cost-effectiveness of EVAR with conventional open repair for AAA.

Methods

Patients: 1,252 patients from 37 centres in the UK.

Inclusion criteria:

- Aged ≥ 60 y;
- Asymptomatic AAA of at least 5.5cm in diameter;
- Aneurysm morphology suitable for EVAR;
- Fit for open repair.

Groups:

- EVAR ($n = 626$);
- Open repair ($n = 626$).

Primary endpoint: All-cause mortality.

Secondary endpoints:

- Aneurysm-related mortality;
- HRQOL;
- Post-operative complications;
- Hospital costs.

Follow-up: Median F/U 6y:

- EVAR: CT scan at 1 and 3mo post-operatively, and then annually;
- Open repair: Annual CT scan.

Results

Table 33.8 Summary of results

| | | EVAR* | Open repair* | p |
|--------------------------------|--------------|---------------|---------------|---------|
| Any death | All patients | 260/626 (7.5) | 264/626 (7.7) | 0.72 |
| | 0–6mo | 26/626 (8.5) | 45/626 (15.0) | 0.06 |
| | >6mo–4y | 125/599 (6.7) | 116/581 (6.3) | 0.39 |
| | >4y | 109/472 (8.4) | 103/461 (7.9) | 0.57 |
| Aneurysm-related death | All patients | 36/626 (1.0) | 40/626 (1.2) | 0.73 |
| | 0–6mo | 14/626 (4.6) | 30/626 (10.0) | 0.03 |
| | >6mo–4y | 12/599 (0.6) | 8/581 (0.4) | 0.44 |
| | >4y | 10/472 (0.8) | 2/461 (0.2) | 0.05 |
| Post-operative complications** | | 45.0% (12.6) | 12.5% (2.5) | <0.0001 |
| Re-interventions** | | 23.2% (5.1) | 8.8% (1.7) | <0.0001 |

* Values (n = 626) No/total (rate/100 person-years). ** Values at end of F/U. p-value relates to rate/100 person-years.

- 30d mortality 1.8% (EVAR) and 4.3% (open surgery);
- Although the open repair group had a diminished HRQOL at 3mo, it had recovered by 12mo; 12–24mo after randomization, there was no difference between the groups;
- Total cost per patient estimated £13,019 (EVAR) and £11,842 (open repair)—£1,177 difference. (See Table 33.8.)

Discussion

EVAR conferred a 3% 30d operative mortality benefit over open aneurysm repair. A 2% aneurysm-related mortality benefit in the EVAR group was noted 4y post-procedure, though it reduced to 0.6% subsequently. However, there was no significant difference in all-cause mortality 4 and 6y post-procedure. In view of late complications within the EVAR group, there remains demand for long-term surveillance, predominantly using CT. This has implications on cost.

Problems

- Interpretation different if the primary endpoint was aneurysm-related mortality, not all-cause mortality.
- Intervention on type II endoleaks may skew data.
- Early generation of devices, imaging technology, and lack of clinical experience may reduce the applicability with contemporary practice.
- Laparotomy-related complications with open surgery not measured.
- Cost analysis not applicable, as many centres moving to the US F/U model. Cost of laparotomy-related complications not included.

Further reading

EVAR 2 (2010). *N Engl J Med* 362, 1872–80.

Peripheral arterial disease: surgery vs angioplasty

BASIL (Bypass versus Angioplasty in Severe Ischaemia of the Leg):

An intention-to-treat analysis of amputation-free and overall survival in patients randomized to a bypass surgery-first or a balloon angioplasty-first revascularization strategy.

AUTHORS: Bradbury A, Adam D, Bell J et al.

REFERENCE: *J Vasc Surg* (2010) 51, 5S–17S.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Bypass surgery and balloon angioplasty are equally effective first-line treatments for severe ischaemia of the leg due to infra-inguinal disease. However, for patients who survive for >2y after treatment, bypass was associated with a significant increase in overall survival, though it was more expensive than angioplasty.

Impact

Fitter, younger patients with severe lower limb ischaemia are probably better off having surgery as the first approach. Those patients with severe co-morbidities may be best advised towards angioplasty as a first-line treatment.

Aims

The treatment of critical limb ischaemia remains controversial, with advocates for surgical or endovascular therapies based on personal preference. This study aimed to compare the outcomes of a surgery-first with an angioplasty-first strategy in patients with severe leg ischaemia.

Methods

Patients: 452 patients from 27 centres in the UK.

Inclusion criteria:

- Severe limb ischaemia (rest pain or tissue loss >2wk);
- Infra-inguinal disease amenable to both types of treatment.

Groups:

- Surgery-first ($n = 228$ randomized; $n = 195$ (86%) attempted intervention);
- Angioplasty-first ($n = 224$ randomized; $n = 216$ (96%) intervention).

Primary endpoint: Amputation-free survival (alive with trial leg intact).

Secondary endpoints:

- All-cause mortality;
- 30d morbidity and mortality;
- Re-interventions;
- HRQOL;
- Use of hospital resources.

Follow-up: Mean F/U 3.1y.

Results

Table 33.9 Summary of results

| | Angioplasty (n = 224) | Bypass (n = 228) | p |
|--|--------------------------|---------------------|-------|
| Amputation-free survival at 1y | 71% | 68% | |
| Amputation-free survival at 3y | 52% | 57% | |
| Amputation-free survival at final F/U | 37% | 38% | |
| Adjusted HR of surgery vs angioplasty for overall survival, | <2y = 1.19 | >2y = 0.61 | 0.011 |
| 30d mortality | 3% | 5% | |
| 30d morbidity | 41% | 57% | |
| Re-intervention rate | 36% | 26% | |
| Inpatient annual treatment cost | £17,419 | £23,322 | |

- Patients in the bypass group who survived 2y gained 7mo life expectancy (significant) and 6mo amputation-free life expectancy (non-significant);
- By 3y, 36% following angioplasty had clinical failure and went on to have a second intervention (surgery in most cases);
- No significant differences in HRQOL between the groups, and overall improvement by 3mo largely sustained during F/U;
- At end F/U, 56% had died (equal in two treatment groups). (See Table 33.9.)

Discussion

Angioplasty and surgery had broadly similar outcomes, in terms of amputation-free survival. Angioplasty provided a less durable result, requiring more re-interventions, but was cheaper than surgery, with fewer periprocedural complications. Angioplasty is therefore often the first choice for patients with significant co-morbidities and short life expectancy. Surgery provided a more durable result and may be appropriate for younger, healthier individuals. However, failed endovascular procedures did not preclude a subsequent surgical bypass.

Problems

- Suitable patients represented a small fraction of those with the condition. Only 30% of eligible patients were recruited. One-third refused to join the study.
- One-third were not on antiplatelet therapy. Only one-third were on statins.

Peripheral arterial disease: angioplasty vs stenting

ABSOLUTE Trial: Balloon angioplasty vs implantation of nitinol stents in the superficial femoral artery.

AUTHORS: Schillinger M, Sabeti S, Dick P et al.

REFERENCE: *Circulation* (2007) **115**, 2745–9.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Treatment of superficial femoral artery (SFA) disease using self-expanding nitinol (nickel–titanium) stents is associated with superior anatomical and clinical results for up to 2y F/U.

Impact

While these findings potentially change the endovascular treatment of SFA disease, they are not supported by a subsequent Cochrane review.

Aims

Restenosis, particularly in long segments, is a major problem in the endovascular treatment of the SFA. Stainless steel stents are not beneficial to angioplasty (*J Vasc Interv Radiol* (2001) **12**, 935–42). This study aimed to compare the anatomical and clinical outcomes of newer self-expanding nitinol (nickel and titanium alloy) stents with conventional balloon angioplasty.

Methods

Patients: 104 patients (F/U 1y), 98 patients (F/U 2y), at one centre in Austria.

Inclusion criteria:

- Clinically severe claudication or chronic limb ischaemia due to stenosis or occlusion of the SFA;
- Anatomically (based on angiography at the time of the intervention) >50% stenosis or occlusion length >30mm;
- At least one patent run-off vessel.

Exclusion criteria:

- Acute critical limb ischaemia;
- Previous bypass stenting or surgery;
- Untreated iliac artery disease;
- Known intolerance to medications or contrast.

Groups:

- 1° nitinol stent implantation ($n = 46$);
- Angioplasty ($n = 52$).

Primary endpoints: 6mo—restenosis >50% of diameter of treated segment on angiogram; 24mo—assessed by arterial duplex for restenosis.

Secondary endpoints:

- Anatomic: Restenosis >50% (US or angiogram);
- Clinical: Rutherford stage and maximal treadmill walking capacity;
- Haemodynamic: Resting ankle-brachial pressure index (ABPI).

Follow-up: Clinical review at 24h, 3 and 6mo, and 1 and 2y. Duplex US scan at 3, 6, 12, and 24mo. Angiogram (digital subtraction or CT) at 6mo. Data evaluated by two independent observers.

Results**Table 33.10** Summary of results

| Restenosis rate | Stenting (n = 51) | Angioplasty (n = 53) | p |
|-------------------------------|-------------------|----------------------|------|
| 6mo | 24% | 37% | 0.05 |
| 1y | 43% | 63% | 0.01 |
| 2y | 45.7% | 69.2% | 0.03 |
| Treadmill walking capacity 2y | 302m | 196m | 0.12 |
| ABPI reading 2y | 0.88 | 0.78 | 0.09 |

After 2y, four patients had died, and two refused F/U.

- No interaction between treatment group restenosis and peripheral arterial disease stage or length of lesion, indicating the benefit of stenting was not influenced by these. (See Table 33.10.)

Discussion

At 2y, there was a benefit from 1° stenting, compared with angioplasty. This may be explained by the improved radial strength of nitinol, the ability to recover from being crushed, and reduced foreshortening allowing precise placement. Bypass surgery with venous grafts remains the gold standard treatment of chronic limb ischaemia. However, this study suggests that nitinol stents may be an effective alternative for longer lesions in patients who are poor candidates for surgery or who do not have a harvestable saphenous vein. This depends on a low complication rate and ensuring the surgical target zone is unaffected in case subsequent bypass is required. Both requirements were fulfilled in this study.

Problems

- Small study (n = 104, 2y F/U) risks type I error.
- Primary endpoint assessed by computed tomography angiography/digital subtraction angiography (CTA/DSA), although their use in stent stenosis not yet validated.
- Findings conflict with other similar studies, and benefits may be related to antiplatelet regime, rather than stenting.
- A 2009 update (n = 968, eight studies): at 6mo, small, significant improvement in patency, ABPI, and treadmill capacity after angioplasty plus stent vs angioplasty alone. Benefit lost at 12mo. Studies used differing antiplatelet regimes. Therefore, routine stent insertion following angioplasty cannot be recommended.

Further reading

Twine CP, et al. (2009). Angioplasty versus stenting for superficial femoral artery lesions. *Cochrane Database Syst Rev* 2, CD006767.

Varicose veins: surgical technique

Randomized clinical trial comparing endovenous laser ablation, radiofrequency ablation, foam sclerotherapy and surgical stripping for great saphenous varicose veins.

AUTHORS: Rasmussen L, Lawaetz M, Bjoern L et al.

REFERENCE: *Br J Surg* (2011) **98**, 1079–87.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Endovenous laser ablation (EVLA), RFA, foam sclerotherapy (FS), and surgical stripping (SS) are all efficacious treatments for great saphenous vein (GSV) incompetence. The technical failure rate is highest with FS. RFA and FS were associated with faster recovery and reduced pain post-operatively.

Impact

Endovenous ablation is effective for GSV incompetence. Minimally invasive treatments are increasingly common, due to reduced length of stay and perioperative pain.

Aims

Varicose veins (VVs) are common, affecting 25% of Western adults. Traditional surgical treatment comprises junctional ligation, truncal stripping, and phlebectomies. In the past decade, other minimally invasive treatment modalities, including EVLA, RFA, and FS, have gained popularity. This study aimed to compare these new methods against one another and conventional surgery in the same randomized trial.

Methods

Patients: 500 patients (580 legs) at two centres in Denmark.

Inclusion criteria:

- Age 18–75y;
- Symptomatic VV;
- GSV incompetence on duplex imaging;
- Clinical aetiologic anatomic pathophysiology (CEAP) class C2–4.

Exclusion criteria:

- Duplication of the saphenous trunk or incompetent anterior accessory saphenous vein;
- Small saphenous vein reflux;
- Previous DVT;
- History of arterial insufficiency or ABPI <0.9;
- Axial deep vein insufficiency;
- Tortuous GSV unsuitable for endovenous treatment.

Groups:

- EVLA ($n = 125$ patients; $n = 144$ legs);
- RFA ($n = 125$ patients; $n = 148$ legs);

- FS ($n = 125$ patients; $n = 145$ legs);
- SS ($n = 125$ patients; $n = 143$ legs).

Primary endpoint: Technical success (closed/absent GSV with lack of flow).

Secondary endpoints:

- Pain;
- Absence from work and normal activity;
- Scores for the medical outcomes study short form (SF36);
- Venous Clinical Severity Score (VCSS) and Aberdeen Varicose Vein Symptom Severity Score (AVVSS);
- Recurrence rates.

Follow-up: At 3d, 1mo, and 1y post-procedure with duplex US (intention to F/U till 5y).

Results

Table 33.11 Summary of results

| | EVLA | RFA | FS | SS |
|-----------------------------------|-------|-------|-------|-------|
| Failure rate after 3d* | 0% | 0% | 2.1% | 2.8% |
| Failure rate after 1mo* | 0.7% | 0% | 1.4% | 2.2% |
| Failure rate after 1y* | 5.8% | 4.8% | 16.3% | 4.8% |
| Recurrence rate after 1y* | 11.6% | 7.3% | 13.8% | 14.8% |
| Complications in the first month* | 7.6% | 18.2% | 23.4% | 13.3% |
| Total cost (€) | 2,200 | 1,996 | 1,554 | 2,199 |

* Percentage of legs treated.

- Significantly higher failure rate in the FS group ($p < 0.001$), but no difference between the other three groups ($p = 0.543$) (see Table 33.11);
- Complications were mostly minor (e.g. phlebitis, infection, or paraesthesiae). Only two major complications occurred (one DVT and one PE, both in the FS group);
- Patients in the RFA and FS groups reported significantly less pain than those in the EVLA and SS groups ($p < 0.001$) during the first 10d post-procedure;
- Time to resumption of normal activities and work was significantly shorter in the FS and RFA groups, compared to EVLA and SS;
- VCSS and AVVSS scores improved significantly after all treatments.

Discussion

FS had significantly higher technical failure rates. VCSS and AVVSS scores significantly improved after all treatments, with recurrence similar after 1y. SS remains for VVs not amenable to endovenous therapies or when patients decline such treatments.

Problems

- Only 1y F/U; longer-term F/U is needed.
- A total of 20% did not complete the 1y F/U (evenly spread between the groups).

Further reading

Nesbitt C, et al. (2011). *Cochrane Database Syst Rev* 10, CD005624.

Venous ulcers: surgery vs compression

ESCHAR (Effect of Surgery and Compression on venous ulcers Healing And Recurrence): Comparison of surgery and compression with compression alone in chronic venous ulceration.

AUTHORS: Gohel MS, Barwell JR, Taylor M, Chant T et al.

REFERENCE: *BMJ* (2007) 335, 1–6.

STUDY DESIGN: RCT.

EVIDENCE LEVEL: 1b.

Key message

Surgical correction of superficial venous reflux reduces ulcer recurrence at 3y.

Impact

In addition to elastic compression therapy, superficial venous surgery can be considered an essential part of the management strategy for patients with chronic venous ulcers related to superficial venous insufficiency.

Aims

Chronic venous ulcers cause significant morbidity. They have a protracted course of healing, with a high probability of future recurrences. This study aimed to assess the effect of surgery and compression on the healing and recurrence of venous ulcers.

Methods

Patients: 500 patients from three vascular centres in the UK.

Inclusion criteria: Pure venous leg ulcerations:

- Open or recently healed (within the preceding 6mo) ulceration, for longer than 4 wk, between the ankle and the malleoli;
- ABPI >0.85;
- Evidence of superficial venous reflux alone or mixed superficial and deep venous reflux on duplex imaging.

Exclusion criteria:

- Complete occlusion of deep veins on duplex imaging;
- Unfit for surgery;
- Malignant ulcers.

Groups:

- Compression group: Multilayer compression bandaging until ulcer healed, and class 2 elastic compression stockings thereafter ($n = 258$);
- Surgery group: Long or short saphenous disconnection, stripping, and avulsion, in addition to compression hosiery therapy ($n = 242$).

Primary endpoints:

- Ulcer healing rate;
- Ulcer recurrence rate.

Secondary endpoint:

- Ulcer-free time.

Follow-up: 4y F/U report:

- Patients with open ulceration: Reviewed monthly until complete healing occurred;
- After healing: Reviewed at 1mo, then every 3mo until 1y, and every 6mo thereafter.

Results**Table 33.12** Summary of results

| | Compression and surgery | Compression alone | <i>p</i> |
|----------------------------|-------------------------|-------------------|----------|
| 24wk healing rate | 65% | 65% | 0.9 |
| 3y healing rate | 93% | 89% | 0.737 |
| 12mo ulcer recurrence rate | 12% | 28% | <0.001 |
| 4y ulcer recurrence rate | 31% | 56% | <0.001 |
| Ulcer-free time after 3y | 100wk | 85wk | 0.013 |

- Subgroup analysis by venous reflux pattern (incompetent superficial system only, incompetent superficial and deep systems) showed no significant difference in ulcer healing or ulcer recurrence rate. (See Table 33.12.)

Discussion

Ulcer healing was not enhanced by superficial venous surgery and could be achieved by multilayer compression bandaging alone. The main benefit of surgery was in reducing ulcer recurrence.

Problems

- There was poor compliance with surgical treatment, with 24% of patients randomized to surgery refusing to attend for their operation.
- Patients waited a median of 7wk for their operation and therefore may not have achieved an immediate benefit.
- Furthermore, there was no assessment of compliance with the use of compression stockings.

Index

- 3-CPO 174–5
 4S (Scandinavian Simvastatin Survival Study) 58–9
- A**
- abacavir, HIV 322–3
 Abdalla, M 556–7
 abdominal aortic aneurysm (AAA) 898
 endovascular vs
 open repair in 'fit' patients 914–15
 screening 910–11
 small aortic
 aneurysms 912–13
 abdominal surgery,
 enhanced recovery
 following 554–5
 ABSOLUTE 918–19
 absolute risk reduction (ARR) 47
 ACCENT II 235
 'accessing' step, EBM process 38–41
 ACCORD 135, 138–9
 acenocoumarol, venous thromboembolism 310–11
 acetic acid, otitis externa 768–9
 N-acetylcysteine, alcoholic hepatitis 228–9
 aciclovir (ACV)
 Bell's palsy 384–5
 genital herpes
 prophylaxis 256–7
 treatment 254–5
 ocular herpes
 simplex 762–3
 acitretin 102
 acne
 isotretinoin 102, 118–19
 systemic retinoids 118–19
 acromegaly
 octreotide 198–9
 pegvisomant 200–1
 ACST-1 900–1
 ACTG A5202 322–3
 ACTG A5221 326–7
 acute coronary syndrome (ACS), non-ST see non-ST elevation acute coronary syndrome
 acute respiratory distress syndrome (ARDS)
 femoral fracture 848–9
 high-frequency oscillation for 660–1
 prone positioning in 650
 AD2000 276–7
 adalimumab, rheumatoid arthritis 488–9, 493
 Adam, D 916–17
 Adamina, M 554–5
 Adamus, J 798–9
 adaptive pacing therapy (APT) 416–17
 Addison, Thomas 180
 Addison's disease 180
 adenoidectomy
 otitis media with effusion 774–5
 recurrent upper respiratory tract infections in children 782–3
 adenoma 182–3
 adenotonsillectomy 788–9
 adrenaline, peptic ulcer disease 216, 217
 adriamycin, breast cancer 583
 AFFIRM 98–9
 age-related macular degeneration (AMD) 738
 bevacizumab 750–1
 ranibizumab 748–51
 vascular endothelial growth factor antagonists 748–9
 AGIS-7 740–1
 Aircast brace 166–7
 Albala, D 884–5
 albumin following paracentesis 230–1
 albuterol, virus-induced wheeze 530
 alcoholic hepatitis (AH)
 combination therapy 228–9
 corticosteroids 226–7
 alemtuzumab, kidney transplantation 824–5
 alendronate,
 osteoporosis 192–3
 Alenezi, F 664–5
 alfentanil, analgesia in children 159
 Alhazzani, W 664–5
 ALIFE 716–17
 all-trans-retinoic acid (ATRA), acute promyelocytic leukaemia 304–5
 Allan, B 760–1
 Allart, C 494–5
 Allen & Hanburys Ltd UK Study Group 454–5
 allopathy–homeopathy boundary 17
 Allum, W 620–1
 ALMANAC 571
 ALMS
 first phase—induction therapy 438–9
 second phase—maintenance therapy 440–1
 Altman, D 720–1
 Alzheimer's disease (AD)
 antipsychotics and cognitive decline 280–1
 donepezil 276–7
 memantine 278–9
 preventing progression from mild cognitive impairment 274–5
 aminophylline, chronic obstructive pulmonary disease 466
 amiodarone, heart failure 92–3
 amitriptyline, peripheral neuropathy 383
 amlodipine,
 hypertension 60–1
 ampicillin resistance 338
 amyotrophic lateral sclerosis (ALS) 378–9
 anaemia 426–7
 anaesthesia 537–57, 674
 carotid endarterectomy 904–5
 depth of 548–9
 analgesia
 epidural 550–1
 nasal diamorphine in children 158–9
 renal colic 880–1
 anastrozole
 early breast cancer 584–5
 prevention of breast cancer 566–7
 Anderson, D 176–7
 Anderson, G 728–9
 Anderson, IM 390–1
 Anderson, J 462–3
 Anderson, S 568–9
 Andrews, DW 690–1

- Andry, Nicholas 840
- angina
 placebos 18–19
 surgery vs best medical therapy 594–5
- angioplasty
 balloon *see* balloon
 angioplasty
 coronary artery
 disease 596–7
- angiotensin-converting enzyme inhibitors (ACE-Is) 434–5
- angiotensin II receptor antagonists 90–1
- Anh Ho, V 338–9
- ankle injury imaging 154–5
- ankle sprain
 management 166–7
- ankylosing spondylitis 500–1
- Annane, D 668–9
- anorexia nervosa 412–13
- anterior cruciate ligament (ACL)
 reconstruction 854–5
- anthracycline, breast cancer 578–9, 587
- anti-angiogenic treatment, colorectal cancer 636–7
- antibiotics
 prophylaxis
 gastrointestinal bleeding with cirrhosis 224–5
 pancreatitis, acute 628–9
 resistance 246–7
 therapy
 bacterial vaginosis 260–1
 brucellosis 340–1
 chlamydia 248–9
 enteric fever 338–9
 Lyme disease 342–3
 otitis media, acute 770–1
 preterm rupture of membranes and spontaneous labour 722–3
 rhinosinusitis, acute 780–1
 sore throat, acute, in children 786–7
 syphilis 244–5
 tuberculosis 330
- anticholinergics, chronic obstructive pulmonary disease 460–1
- antidepressants
 depression
 relapse
 prevention 392–3
 SSRIs vs TCAs 390–1
 panic disorder 408–9
 peripheral neuropathy 383
- antiepileptic drugs (AEDs)
see antipsychotics
- antiphospholipid antibodies, recurrent miscarriage 714–15
- antiplatelet bleeding risk management, peptic ulcer disease 214–15
- antiplatelet drugs, stroke 356–7
- antipsychotics
 epilepsy
 generalized and unclassifiable 364–5
 introduction of medication 358–9
 partial-onset 362–3
 withdrawal of medication 360–1
- older people
 Alzheimer's disease 280–1
- epilepsy,
 new-onset 282–3
- schizophrenia
 atypical vs typical antipsychotics 400–1
 relapse
 prevention 402–3
 treatment-resistant 404–5
- antireflux surgery
 laparoscopic vs medical management 614–15
 laparoscopic vs open fundoplication 616–17
- antiretroviral therapy *see* under HIV
- antisepsis 14, 674
- antithymocyte globulin (ATG), kidney transplantation 824–5
- antiviral therapy,
 genital herpes
 prophylaxis 256–7
 treatment 254–5
- aortic stenosis 608–9
- aortic valve
 replacement (AVR)
 aortic stenosis 608–9
 mechanical vs biological valve 606–7
- Apfel, C 556–7
- apnoea of
 prematurity 514–15
- APPE 220–1
- Appelman, C 770–1
- applying evidence to your patient 50–1
- 'applying' step, EBM process 41
- appraising and reporting checklists 41
- 'appraising critically' step, EBM process 41
- AQUAMAT 336–7
- argon laser photocoagulation, diabetic retinopathy 752–3
- macular oedema 754–5
- Aribisala, B 144–5
- Arican, O 252–3
- arithmetic tradition 9
- Armstrong, PW 64–5
- aromatase inhibitors (AIs)
 early breast cancer 584–5
 prevention of breast cancer 566–7
- arsenic trioxide (ATO), acute promyelocytic leukaemia 304–5
- artesunate, falciparum malaria 330, 334–7
- arthritis
 cardiovascular outcomes with drug therapies 498–9
 gouty 502–3
 rheumatoid *see* rheumatoid arthritis
- arthrodesis 698–9
- ARTS 599
- Asberg, A 836–7
- ascites 230–1
- ASCOT-BPLA 60–1
- Ashcroft, D 110–11
- 'asking' step, EBM process 36–8
- asphyxial encephalopathy, perinatal 516–17
- aspirin
 Alzheimer's disease 277
 arthritis 498
 atrial fibrillation 266–7
 carotid artery
 stenosis 902, 908
 Kawasaki disease 528
 macular oedema in diabetic retinopathy 754–5
 miscarriage, recurrent antiphospholipid antibodies 714–15
 unexplained 716–17
 myocardial infarction 62–3, 64
 non-ST elevation ACS 70, 72–3, 74–5
 peptic ulcer disease 214–15
 stroke 356–7
- 'assessing' step, EBM process 41
- Assimos, D 884–5

- asthma 448
 early inhaled steroid 452–3
 leukotriene receptor
 antagonists 456–7
 long-acting β_2 agonist and
 inhaled steroid 454–5
 self-management 450–1
 astrocytoma, adjuvant
 temozolomide for grade 4
 692–3
 ATAC 584–5
 Ataie, L 184–5
 atazanavir, HIV 322–3
 atenolol, hypertension 60–1
 Atkin, W 208–9
 atomoxetine,
 ADHD 414–15
 atopic eczema 102
 systemic treatment with
 methotrexate vs
 azathioprine 106–7
 topical proactive
 treatment 104–5
 atrial fibrillation (AF)
 rate vs rhythm
 control 98–9
 warfarin 266–7
 Attanasio, R 198–9
 attention-deficit/hyperactivity
 disorder (ADHD) 414–15
 ATTRACT 492–3
 Attwood, S 614–15
 autosomal dominant
 polycystic kidney disease
 (ADPKD) 442–3
 autotitrating positive
 airway pressure (APAP),
 obstructive sleep
 apnoea 790–1
 Avvisati, G 304–5
 axillary surgery 570–1
 azacytidine,
 myelodysplasia 306–7
 azathioprine (AZA) 102
 atopic eczema 106–7
 diabetes mellitus 132
 kidney
 transplantation 816–17
 lupus nephritis 440–1
 renal vasculitis 444
 azithromycin
 chlamydia 248–9
 enteric fever 338–9
 resistance 246, 247
 Azizi, F 184–5
 Azzopardi, D 516–17
- B**
 B-Aware! 548–9
 B-cell-targeted therapy, rheu-
 matoid arthritis 496–7
 Bachmann, LM 154–5
 back pain, lower 696–7
 Backonja, M 382–3
 Bacon, Francis 6
 bacterial vaginosis
 (BV) 260–1
 BAFTA 266–7
 Baker, RI 308–9
 Baldessarini, R 398–9
 Balfour, Thomas Graham 12
 Ballard, C 280–1
 Ballonius 486
 balloon angioplasty 898
 peripheral arterial disease
 vs stenting 918–19
 vs surgery 916–17
 Bandello, F 758–9
 Banducci, D 810–11
 Bang, N 332–3
 Barbarash, R 254–5
 Bardy, G 92–3
 bare-metal stents
 (BMS) 898
 coronary artery
 disease 78–9
 in multivessel disease 85
 vs surgery 598–9
 BARI 596–7
 BARI 2D 80–1
 bariatric surgery 140–1, 145
 Barker, F 778–9
 Barnard, Christiaan 816–17
 Barnes, M 784–5
 Barnhart, H 732–3
 Barwell, JR 922–3
 basal cell carcinoma (BCC),
 facial 802–3
 BASIL 916–17
 basiliximab, kidney
 transplantation 824–5
 Bassi, C 630–1
 Bauersachs, R 310–11
 Baum, M 584–5
 Baumgaertner, M 844–5
 Bautista, O 874–5
 Bautista, R 164–5
 Beck, A 406–7
 Beck, G 424–5
 Becker, RC 70–1
 beclomethasone dipropion-
 ate (BDP), asthma
 and long-acting β_2
 agonist 454–5
 self-management 450
 Beecher, HK 26–7
 behaviour therapy (BT)
 ADHD 414–15
 bulimia nervosa 410–11
 Behnke, K 408–9
 belatacept, kidney
 transplantation 820–1
 Belfort, R 758–9
 Bell, J 916–17
 Bell's palsy 384–5
 belladonna, scarlet fever 12
 below-knee cast 166–7
 bendrolumethiazide (BFZ),
 hypertension 60–1
 BENEFIT 820–1
 BENEFIT-EXT 821
 Benichou, J 120–1
 benign paroxysmal positional
 vertigo (BPPV) 776–7
 benign prostatic hyperplasia
 (BPH) 874–5
 benserazide, Parkinson's
 disease 374
 Bensimon, G 378–9
 benzathine penicillin,
 syphilis 244–5
 benztropine,
 schizophrenia 404
 Berenholtz, S 654–5
 Berg, K 58–9
 Berkowitz, S 310–11
 Bernard, B 224–5
 Bernard, Claude 13
 Berry, W 544–5
 BeSt 494–5
 β -blockers
 heart failure 86–7
 variceal bleeding 222–3
 β_2 agonists
 asthma 454–5
 chronic obstructive
 pulmonary
 disease 462–3
 betaxolol, glaucoma 746
 Bethel, M 134–5
 bevacizumab
 age-related macular
 degeneration 750–1
 colorectal cancer 636–7
 gastro-oesophageal
 cancer 621
 Beydoun, A 382–3
 Bhandari, M 862–3
 bias
 quality assessment 43
 types 44
 Big Lung Trial 480–1
 Bigelow, Wilfred
 Gordon 592
 Bilezikian, J 188–9
 Bilgic, K 252–3
 Bill-Axelson, A 890–1
 Bingel, Adolf 18–20
 biological heart valve vs
 mechanical valve 606–7
 bipolar disorder 398–9
 Bischoff-Ferrari, H 270–1
 Bishop, J 464–5
 bisoprolol, heart
 failure 86–7

- bispectral index (BIS)
monitoring, depth of
anaesthesia 548–9
- bisphosphonates
for bone metastasis in
breast cancer 588–9
osteoporosis, post-
menopausal 192–3
Paget's disease 194–5
- bivalirudin, non-ST
elevation acute coronary
syndrome 73
- Bjoern, L 920–1
- Bjork–Shiley mechanical
heart valve 606–7
- Black, D 192–3
- Black, N 772–3
- bladder cancer
haematuria
assessment 892–3
post-operative intravesical
therapy 894–5
- Blajchman, M 290–1
- Blane, Sir Gilbert 8
- Bledsoe boot 166–7
- bleeding, traumatic 542–3
- blinding, and quality
assessment 43
- blood pressure control
chronic kidney
disease 424–5
diabetes mellitus 138–9
- Bloomfield, P 606–7
- Blum, R 478–9
- Blume, WT 704–5
- boceprevir, hepatitis 238
in HIV-positive
individuals 324–5
- Boden, WE 76–7, 78–9
- Bogner, HR 396–7
- Boice, J 502–3
- Bone, L 848–9
- bone marrow transplant
(BMT) 296–7
- bone metastasis 588–9
- Boonacker, CWB 782–3
- Bosch, A 218–19
- Bouzamondo, A 256–7
- Boyle, Robert 6
- BR.21 study 482–3
- Bradbury, A 916–17
- BRAF inhibitors 124–5
- brain metastases, and
radiosurgery 690–1
- branch retinal vein occlusion
(BRVO) 758–9
- Brandt, J 500–1
- BRANT 682–3
- BRAT 685
- Braun, J 500–1
- breast cancer 559–89
axillary surgery 570–1
and long-acting $\beta 2$
agonist 455
self-management 450, 451
- Budjai, A 70–1
- bulimia nervosa
cognitive vs stand-
ard behavioural
therapy 410–11
family therapy 412–13
- bullous pemphigoid
(BP) 120–1
- Bunce, C 760–1
- Bundgaard, M 162–3
- bupropion, smoking
cessation 470–1
- burn scars,
hypertrophic 804–5
- Burr, M 458–9
- Burza, M 140–1
- Buse, J 142–3
- Busse, W 452–3
- Butkus, D 118–19
- Byington, R 136–7, 138–9
- bypass surgery, peripheral
arterial disease 916–17
- C**
- cabergoline
acromegaly 199
hyperprolactinaemia 202–3
- CABRI 597
- caesarean section
(CS) for breech
presentation 726–7
caffeine therapy 514–15
- calcineurin inhibitors (CNIs)
atopic eczema 104–5
kidney transplanta-
tion 822–3, 826
- calcipotriol,
psoriasis 110–11
- calcitriol, psoriasis 110, 111
- calorie restriction,
T2DM 144–5
- Calverley, P 462–3
- Campanini, A 790–1
- Campbell, I 458–9
- Canadian C-spine rule 152–3
- Canadian Orthopaedic
Trauma Society 864–5
- candesartan, heart
failure 90–1
- Candiotti, KA 552–3
- Cannon, C 498–9
- capecitabine
gastro-oesophageal
cancer 621
pancreatic cancer 631
- CAPRICORN 87
- Caravita, T 302–3
- carbamazepine (CBZ)
- bisphosphonates for bone
metastasis 588–9
- breast-conserving surgery
vs mastectomy 568–9
- chemotherapy 578–9,
583, 587
bone metastasis 589
timing 580–1
- endocrine therapy 584–5
- herceptin 586–7
- hormone replacement
therapy 729
- oncological safety of
immediate breast
reconstruction 572–3
- prevention
anastrozole 566–7
tamoxifen 564–5,
566, 567
- radiotherapy
and breast-conserving
surgery 574–5
for *in situ* cancer 576–7
- screening 560
benefit vs harm 562–3
- tamoxifen
for early cancer 582–3
for prevention 564–5,
566, 567
- breast-conserving surgery
see *under* breast surgery
- breast reconstruction
572–3
- breast surgery 559–89
augmentation 808–9
- breast-conserving
surgery (BCS)
ductal carcinoma *in situ* 576–7
vs mastectomy 568–9
and radiotherapy 574–7
- reconstruction 572–3
reduction 810–11
- Bredland, T 842–3
- breech presentation 726–7
- Breedveld, F 488–9, 492–3
- Brenner, B 310–11
- Brière, J 300–1
- Brighen, S 302–3
- bromocriptine, hyperprolac-
tinaemia 202–3
- Brooks, D 374–5
- Brophy R 856–7
- Brown-Séquard,
Charles-Edouard 180
- Browning, G 772–3
- brucellosis 340–1
- Bryant, J 568–9
- Buck, G 296–7
- budesonide, asthma
early intervention
452–3

- new-onset epilepsy 282–3
- partial-onset
 - epilepsy 362–3
- carbidopa, Parkinson's disease 376
- carboplatin, non-small cell lung cancer 481
- cardiac arrest
 - hypothermia after 170–1
 - therapeutic hypothermia after 670–1
- cardiac resynchronization therapy (CRT) 94–5
- cardiac surgery 591–609
- cardiac
 - transplantation 816–17
- cardiology 55–99
- cardiopulmonary exercise (CPX) testing, preoperative 540–1
- cardiovascular risk
 - arthritis 498–9
 - bariatric surgery in diabetes 140–1
 - chronic kidney disease
 - erythropoietin-stimulating agents 426–7
 - statins and ezetimibe 428–9
 - cinacalcet 432–3
 - hormone replacement therapy 729
 - preoperative cardiopulmonary exercise testing 540–1
- CARE-HF 94–5
- care home placement, assessment before 284–5
- Carithers, RJ 226–7
- Carney, S 392–3
- carotid artery disease 898
- carotid artery stenosis
 - endarterectomy
 - asymptomatic 900–1
 - vs stenting 906–9
 - symptomatic 902–3
 - general vs local anaesthetic 904–5
- carotid endarterectomy (CEA) 898
 - asymptomatic 900–1
 - general vs local anaesthetic 904–5
 - vs stenting 906–9
 - symptomatic 902–3
- Carpenter, W 402–3
- Carrel, Alexis 898
- Carroli, G 720–1
- carvedilol, heart failure 87
- Cascinelli, N 798–9
- case studies, importance of 10
- CAST 166–7
- cataracts 738
- catecholamines, septic shock 652–3
- catheter-related bloodstream infections (CRBSIs), reducing 654–5
- CATIE 400–1
- CATT 750–1
- cefexime resistance 246, 247
- cefotaxime, pelvic inflammatory disease 258–9
- ceftriaxone
 - Lyme disease 342–3
 - resistance 246, 247
 - typhoid fever 339
- Celli, B 462–3
- cellulitis, recurrent 122–3
- central retinal vein occlusion (CRVO) 758–9
- cephalosporins
 - pelvic inflammatory disease 258–9
 - resistance 246
- cerebral palsy 514–15
- cervical cancer 250–1
- cervical cerclage 718–19
- cervical spine trauma
 - imaging 152–3
- CESAR 656–7
- cetuximab, colorectal cancer 637
- Chaisson, C 856–7
- CHALICE 156–7
- Challis, D 284–5
- Chamberlen brothers 708
- Chan, F 214–15
- Chandratheva, A 354–5
- Chant, T 922–3
- Chapman, P 124–5
- Chapman, TL 436–7
- Charbonnier, B 474–5
- Charlton, M 892–3
- CHARM 90–1
- Charnley, Sir John 840
- Charpentier, B 820–1
- chemotherapy
 - astrocytoma, grade 4 692–3
 - bladder cancer 894–5
 - breast cancer 578–9, 583, 587
 - bone metastasis 589
 - timing 580–1
 - colorectal cancer 636–7
 - gastro-oesophageal cancer 620–1
 - lung cancer
 - non-small cell 480–1, 482–3
 - small cell 478–9
 - oesophageal cancer 618–19
 - pancreatic cancer 630–1
 - prostate cancer 889
 - rectal cancer 638, 639, 640–1
 - long-course chemoradiotherapy 642–3
- Chen, Y 316–17
- Cheng, W 244–5
- Chervinsky, P 456–7
- Cheselden, William 10
- children see paediatrics
- Ching, J 214–15
- Chittock, D 658–9
- Chiu, D 906–7
- chlamydia 248–9
- chlorambucil, membranous nephropathy 436–7
- chloramphenicol resistance 338
- chlorpromazine, schizophrenia 404, 405
- chlortetracycline, syphilis 244
- cholecystectomy 624–5
- cholecystitis, acute 624–5
- cholera 13–14
- cholinesterase inhibitors (CHEIs), Alzheimer's disease 276, 277, 281
- CHOP chemotherapy, diffuse large B-cell lymphoma 300–1
- Christiansen, P 408–9
- Chrolavicius, S 68–9
- chronic fatigue syndrome (CFS) 416–17
- chronic kidney disease see kidney disease, chronic
- chronic obstructive pulmonary disease (COPD)
 - inhaled steroids and long-acting β_2 agonists 462–3
 - long-acting anticholinergic 460–1
 - long-term oxygen therapy 464–5
 - non-invasive ventilation 466–7
 - pulmonary rehabilitation 458–9
 - and smoking 448
- chronic pain
 - management 538
- chronology of EBM 30–1

- CIBIS II 86–7
 ciclosporin (CsA) 102
 diabetes mellitus 132
 membranous
 nephropathy 436–7
 psoriasis 112–13
 rheumatoid arthritis 495
 transplantation 816–17
 kidney 820–1, 822–3, 826
 ulcerative colitis 232–3
 CIGTS 742–3
 cinacalcet
 cardiovascular
 effects 432–3
 primary hyperparathyroidism 188–9
 Cinahl 40
 cinchona bark 6
 ciprofloxacin
 pancreatitis,
 acute 628, 629
 resistance 247
 cirrhosis with gastrointestinal
 bleeding 224–5
 cisplatin
 gastro-oesophageal
 cancer 620–1
 lung cancer
 non-small cell 480–1
 small cell 478–9
 oesophageal
 cancer 618–19
 Ciuleanu, T 482–3
 Clark, D 406–7
 Clark, T 464–5
 Clarke, P 546–7
 Clarke, WR 686–7
 Clarkson, P 284–5
 CLASICC 634–5
 clavicle fractures,
 mid-shaft 864–5
 Clayman, R 884–5
 Cleland, J 94–5
 Clements, P 504–5
 Cleveland Clinic
 Study 602–3
 clindamycin, bacterial
 vaginosis 260–1
 clinical experience,
 primacy of 6–7
 clinical practice
 guidelines 50–1
 clinical trials, design
 issues 18–20
 clipping for ruptured
 intracranial
 aneurysms 684–5
 clobetasol propionate,
 bullous pemphigoid 120
 clomiphene, polycystic ovary
 syndrome 732–3
 clopidogrel
 carotid artery stenosis 908
 myocardial
 infarction 62–3, 64
 non-ST elevation ACS 70,
 73, 74–5
 peptic ulcer
 disease 214–15
 stroke 356–7
 Close, J 268–9
 clozapine,
 schizophrenia 404–5
 co-amoxiclav, preterm
 rupture of membranes
 and spontaneous
 labour 722–3
 Cochran, A 800–1
 Cochrane, Archie
 development of EBM 34
 *Effectiveness and
 efficiency* 22–3, 34
 Cochrane database 51
 Cochrane Library 40–1
 cognitive behavioural
 therapy (CBT) 406
 bulimia nervosa 410–11
 chronic fatigue
 syndrome 416–17
 cognitive therapy (CT), panic
 disorder 406–7, 408–9
 Cohen, H 714–15
 Cohen, M 72–3, 316–17
 Coiffier, B 300–1
 coiling for ruptured intracra-
 nial aneurysms 684–5
 Colebrook, Dora 19–20
 Coleman, D 808–9
 Collins, J 282–3
 Collinson, F 634–5
 Colombo, A 218–19
 colonic surgery, enhanced
 recovery 646–7
 colorectal cancer (CRC)
 anti-angiogenic
 treatment 636–7
 hormone replacement
 therapy 729
 once-only flex-
 ible sigmoidoscopy
 screening 208–9
 open vs laparoscopic
 surgery 634–5
 screening 632–3
 colposuspension 872, 873
 COMET 87
 COMMIT 62–3
 comparisons, making 6–7
 compliance therapy,
 schizophrenia 402
 compression therapy, venous
 ulcers 922–3
 computed tomography (CT)
 paediatric head
 injury 156–7
 renal colic 878–9
 urogram 893
 confidence intervals (CI) 12
 95% 48
 Connor, E 524–5
 consent xl
 paediatrics 512–13
 CONSORT 42–4
 Contagious Diseases Act
 1864 242
 continuous positive airways
 pressure (CPAP)
 acute cardiogenic pulmo-
 nary oedema 174–5
 nasal (nCPAP), obstructive
 sleep apnoea 476–7
 CoolCap 516, 517
 COPERNICUS 87
 cor pulmonale 464–5
 coronary angiography 76–7
 coronary artery bypass
 graft (CABG)
 vs angioplasty 596–7
 vs bare-metal stent 598–9
 vs best medical
 therapy 594–5
 conduits 602–3
 coronary artery disease
 in diabetes 82–3
 in multivessel
 disease 84–5
 vs drug-eluting
 stent 600–1
 heart failure 96–7
 off-pump vs on-pump
 bypass 604–5
 coronary artery
 disease (CAD)
 percutaneous coronary
 intervention 78–9
 vs CABG in
 diabetes 82–3
 vs CABG in multivessel
 disease 84–5
 revascularization vs
 medical care in
 diabetes 80–1
 statins 58–9
 surgery
 vs angioplasty 596–7
 vs bare-metal
 stent 598–9
 vs best medical
 therapy 594–5
 vs drug-eluting
 stent 600–1
 coronary bypass graft
 arterial vs venous 602–3
 see also coronary artery
 bypass graft

Correa, C 574–5
 Corrigan, T 472–3
 corticosteroids
 alcoholic hepatitis 226–7
 asthma
 early intervention 452–3
 and long-acting β_2 agonist 454–5
 atopic eczema 104–5
 bullous pemphigoid 120–1
 chronic obstructive pulmonary disease 462–3
 head injury 676–7
 Kawasaki disease 528–9
 liver transplantation 834–5
 multiple sclerosis 370–1
 otitis externa 768–9
 rheumatoid arthritis 494
 rhinosinusitis with nasal polyposis 784–5
 septic shock 668–9
 shoulder pain 506–7
 spinal injury 677
 tuberculosis
 meningitis 330, 332–3
 virus-induced
 wheeze 530–1
 CORTICUS 668–9
 Cosgrove, D 602–3
 COSS 686–7
 Costantino, J 564–5
 COURAGE 78–9
 COX-2 inhibitors,
 gout 502–3
 Cozzi, R 198–9
 CRASH 676–7
 CRASH-2 164–5, 542
 Crawford, J 846–7
 CREST 906–7
 cricoid pressure, use in laryngoscopy 546–7
 Crohn's disease (CD) 234–5
 Crook, AM 122–3
 Cullen, William 16–17
 Cummings, S 192–3
 Cunin, G 368–9
 Cunningham, D 620–1
 CURE 74–5
 Curtin, S 844–5
 Curtis, S 498–9
 Cuschieri, A 622–3
 Cushing, Harvey 180, 674
 Cushman, W 138–9
 CUTLASS 1 401
 Czuzik, J 566–7, 584–5
 Cuzin, L 320–1
 cyclophosphamide
 breast cancer 578–9, 583
 lung cancer 479
 lupus nephritis 438–9

membranous
 nephropathy 437
 renal vasculitis 444
 rheumatoid arthritis 497
 scleroderma lung disease 504–5
 Cypel, M 832–3
 cyproterone acetate,
 prostate cancer 889
 cystic fibrosis (CF) 518–19
 cystoscopy 892–3
 cytarabine, chronic myeloid leukaemia 298–9
 cytomegalovirus (CMV)
 antivirals 836–7
 ganciclovir 526–7

D

D-dimer testing 176–7
 D'Haens, G 232–3
 Daar, E 322–3
 dacarbazine, metastatic melanoma 124, 125
 daclizumab
 diabetes mellitus 132
 transplantation
 kidney 823
 liver 834, 835
 Dahlof, B 60–1
 Daikh, D 502–3
 Dale, Henry 180
 Dallan, I 790–1
 dalteparin, venous thromboembolism in cancer 308
 Dalu, Z 248–9
 Daly, JP 156–7
 dapson, bullous pemphigoid 120
 darbepoetin alfa, chronic kidney disease 426–7
 Darby, S 574–5
 Dare, C 412–13
 darunavir, HIV 320
 dasatinib, chronic myeloid leukaemia 299
 Daubert, J 94–5
 Dave, M 714–15
 David, A 860–1
 Davies, C 392–3, 578–9
 Davies, R 476–7
 Davis, GL 834–5
 Davis, P 514–15
 Dawson-Hughes, B 270–1
 de Melker, RA 786–7
 De Sutter, A 780–1
 de Vries-Bouwstra, J 494–5
 Deakin, J 394–5
 Dean, J 196–7
 decision-making, patient involvement 50
 decompressive surgery
 spinal metastases 688–9
 spondylolisthesis 698–9
 deep-brain stimulation in Parkinson's disease 702–3
 deep vein thrombosis (DVT)
 clinical decision rule and D-dimer testing 176–7
 prophylaxis after pulmonary embolism 472–3
 Deitch, E 804–5
 Delaney, B 212–13
 delirium following hip fracture 272–3
 Dellinger, P 662–3
 dementia
 falls 269
 see also Alzheimer's disease
 Demers, C 72–3
 Demirbas, A 822–3
 Denton, E 878–9
 depression
 antidepressants 390–1
 collaborative care 396–7
 electroconvulsive therapy 394–5
 relapse prevention 392–3
 dermatology 101–25
 Descartes, René 6
 Deuffic-Burban, S 320–1
 development of EBM 34
 developmental dysplasia of the hip (DDH) 842–3
 Devillé, W 506–7
 dexamethasone (DEX)
 and methylprednisolone, equivalent doses 371
 otitis externa 768–9
 post-operative nausea and vomiting 557
 retinal vein occlusion 758–9
 tuberculous meningitis 332–3
 dexamfetamine, ADHD 414–15
 dextran 70 following paracentesis 230–1
 Diabetes Control and Complications Trial 131
 diabetes mellitus 127–47
 coronary artery disease
 PCI vs CABG 82–3
 revascularization vs medical care 80–1
 surgery vs angioplasty 596, 597
 peripheral neuropathy 382–3
 see also type 1 diabetes mellitus; type 2 diabetes mellitus

- diabetic retinopathy 738
 laser photocoagulation 752–3
 macular oedema 754–5
 macular oedema
 laser and vascular
 endothelial growth
 factor antagonists
 for 756–7
 laser photocoagulation 754–5
- Diabetic Retinopathy Clinical Research (DRCR) Network 756–7
- diagnostic studies, statistical tools 49
- dialysis 420
 cardiovascular effects of
 cinacalcet 432–3
 timing of
 intervention 430–1
- diamorphine, analgesia in children 158–9
- diazepam,
 pre-eclampsia 720
- Dick, P 918–19
- diclofenac, arthritis 498–9
- Diener, HC 356–7
- difference between group means 46
- diffuse large B-cell lymphoma (DLBCL) 300–1
- digitalis 6, 10, 56
- digoxin, chronic obstructive pulmonary disease 464
- Dijk, D 604–5
- Dikmen, SS 678–9
- diphtheria 18–20
- dipyridamole, stroke 356–7
- disempowered patient 26
- dislocation in revision total hip replacement 850–1
- distraction
 osteogenesis 860–1
- dithranol, psoriasis 108–9, 110, 111
- Divine, G 190–1
- dizziness, chronic 778–9
- docetaxel, non-small cell lung cancer 483
- Dockhorn, R 456–7
- Doll, Richard 282
- Domanski, M 82–3
- donepezil
 Alzheimer's disease 276–7
 mild cognitive
 impairment 274–5
- Donker, M 576–7
- Donnan, P 384–5
- Doody, R 278–9
- dopamine agonists
 hyperprolactinaemia 202–3
- Parkinson's disease 374–5
- Dotter, CT 898
- double-blind trials 43
- doxapram, chronic obstructive pulmonary disease 466
- doxazosin
 benign prostatic
 hyperplasia 874–5
 hypertension 60
- doxorubicin, small cell lung cancer 479
- doxycycline
 brucellosis 340–1
 chlamydia 248, 249
 Lyme disease 342–3
 pelvic inflammatory
 disease 258–9
 syphilis 244–5
- droperidol, post-operative nausea and vomiting 556, 557
- dropsy 6, 10, 56
- DRS 752–3
- drug-eluting stents (DES) 898
 coronary artery disease
 in diabetes 83
 in multivessel
 disease 84–5
 vs surgery 600–1
- Dubost, Charles 898
- ductal carcinoma *in situ* (DCIS) 576–7
- Duley, F 720–1
- duloxetine
 depression 391
 peripheral neuropathy 383
- Duncan, C 850–1
- Dung, N 332–3
- Dunning, J 156–7
- duodenal ulcer 212–13
- Dupuy, A 256–7
- Dusheiko, G 238–9
- Dutch/Belgian Tiotropium Study Group 460–1
- dynamic hip screw 844–5
- E**
- ear, nose, and throat (ENT)
 see otorhinolaryngology
- Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 560, 578–9, 582–3
- Eastcott, HHG 898
- eating disorders
 cognitive vs standard behavioural
 therapy 410–11
 family therapy 412–13
- Eberlding, E 244–5
- ECASS-3 352–3
- ectopic pregnancy, surgery
 vs methotrexate 712–13
 type 710–11
- eczema see atopic eczema
- EDGE 498
- EDGE II 498
- Edinburgh Valve
 Study 606–7
- Edwards, D 516–17
- Edwards, J 496–7
- Edwards, K 382–3
- Edwards, R 208–9, 734–5
- Edwin Smith papyrus 674
- efavirenz, HIV 322–3
- Ekberg, H 822–3
- El-Sadr, W 318–19
- Elashoff, R 504–5
- elderly people see geriatric medicine; older people
- electroconvulsive
 therapy (ECT),
 depression 394–5
- electronic databases 40
- electrotherapy 19
- ELITE Symphony 822–3
- ELLDOPA 376–7
- Elliott, M 466–7
- Ellis, M 268–9
- emergency
 medicine 149–77
- Emergency Medicine
 Research Society 150
- EMGT 746–7
- emphysema 468–9
- emtricitabine, HIV 322–3
- endocrine therapy 584–5
- endocrinology 179–203
- endometrial cancer
 anastrozole 585
 tamoxifen 582, 583,
 584, 585
- endoscopic retrograde cholangiopancreatography (ERCP) 626–7
- endoscopy
 gastroenterology 206
 peptic ulcer disease,
 bleeding
 control 216–17
 upper gastrointestinal
 bleeding 220–1
 variceal bleeding 222–3
- endovascular aneurysm
 repair (EVAR) 898
 vs open repair in 'fit'
 patients 914–15
- endovenous laser ablation (EVLA) 920–1
- enfuvirtide, HIV 320
- Engelsbel, S 712–13

- enhanced recovery pathways (ERPs)
after abdominal surgery 554–5
after colonic surgery 646–7
- Enlightenment 9
- enoxaparin
myocardial infarction 64
non-ST elevation ACS 68–9, 72–3
venous thromboembolism 310–11
- enteric fever 338–9
- epidermal growth factor receptor (EGFR) inhibitors, non-small cell lung cancer 482–3
- epidural analgesia, safety of 550–1
- epilepsy 348
generalized and unclassified, treatment of 364–5
introduction of medication 358–9
new-onset 282–3
partial-onset, treatment of 362–3
temporal lobe 704–5
withdrawal of medication 360–1
see also seizures
- epinephrine after hip fracture 162
- epirubicin
bladder cancer 894
gastro-oesophageal cancer 620–1
oesophageal cancer 619
- eplerenone, heart failure 89
- Epley's manoeuvre (EM) 776–7
- equipoise 27
- Erdmann, E 94–5
- erectile dysfunction (ED) 876–7
- Eriksen, C 572–3
- erlotinib, non-small cell lung cancer 482–3
- errors, and quality assessment 43
- erythema migrans 342
- erythromycin
chlamydia 248
preterm rupture of membranes and spontaneous labour 722–3
- erythropoietin-stimulating agents, chronic kidney disease 426–7
- ESCHAR 922–3
- esomeprazole
gastro-oesophageal reflux disease 614–15
peptic ulcer disease 214–15
- ESPA-3 630–1
- ESPA-4 631
- ESPRIT 357
- ESPS-2 357
- ESSENCE 72–3
- etanercept, rheumatoid arthritis 490–1
- ETDRS 754–5
- ethambutol, tuberculous meningitis 332
- ethics
choice 26
ethical approval xl
experimentation 26–8
etoposide, small cell lung cancer 478–9
- etoricoxib
arthritis 498–9
gout 502–3
- etravirine, HIV 320
- European Mode of Delivery Collaboration 525
- European Organisation for Research and Treatment of Cancer (EORTC)
breast cancer 576–7
prostate cancer 888–9
- Euvrard, S 826–7
- EVA-3S 908–9
- Evans, E 350–1
- Evans, G 138–9
- EVAR-1 914–15
- everolimus, coronary artery disease 85
- evidence
levels of 39
nature of 4
quality of 39
- evidence-based medicine (EBM)
chronology 30–1
development 34
history 3–31
process 36–41
- EVOLVE 432–3
- ex vivo lung perfusion (EVL) 832–3
- excretory urography 893
- exenatide, diabetes mellitus 142–3
- exercise testing, preoperative 540–1
- experimentation
ethics 26–8
- EXPRESS 114–15, 354–5
- external beam radiotherapy (EBRT) 888–9
- external fixation of long bones 860–1
- extracorporeal lithotripter 870
- extracorporeal membrane oxygenation (ECMO) in adult respiratory failure 656–7
- extracorporeal shock wave lithotripsy (ESWL) 884–5
- extracranial–intracranial (EC–IC) bypass surgery for stroke prevention 686–7
- ezetimibe, chronic kidney disease 428–9

F

- facial basal cell carcinoma 802–3
- faecal occult blood (FOB) screening, colorectal cancer 208, 209, 632–3
- Faetta, G 398–9
- Fahn, S 376–7
- Fairbank, J 696–7
- Fairburn, C 410–11
- Fairnie, D 724–5
- falciparum malaria 330, 334–7
- Falconer, C 872–3
- falls
multifactorial intervention 268–9
vitamin D 270–1
- famciclovir (FCV), genital herpes prophylaxis 256–7
- family therapy (FT), eating disorders 412–13
- Fan, S 624–5
- Farkouh, ME 82–3
- Farrell, P 518–19
- fascia iliaca block after hip fracture 162–3
- fat embolism syndrome 848
- FEAST 532–3
- Fehrenbacher, L 636–7
- Feinstein, Alvan 34
- Fellay, J 344–5
- femoral fracture
neck of femur see hip fracture
timing of surgery 848–9
- Fenaux, P 306–7
- fentanyl
post-operative nausea and vomiting 556
for procedural sedation 160–1

- Fernandes, HM 680–1
 Fernandez-Esparrach, G 230–1
 Ferrier, David 674
 fibroids, uterine 734–5
 Fielding, A 296–7
 Fielding, J 622–3
 Fife, K 254–5
 finasteride
 benign prostatic hyperplasia 874–5
 prostate cancer prevention 886–7
 Finazzi, G 292–3
 Finfer, S 658–9
 fingolimod, multiple sclerosis 373
 FinHer 587
 Fischgrund, JS 698–9
 Fischl, M 322–3
 Fisher, B 564–5, 568–9
 FIT 192–3
 FitzGerald, G 498–9
 Flacker, J 272–3
 Fleming, R 730–1
 Fletcher, K 266–7
 flexible sigmoidoscopy, colorectal cancer 208–9
 flexor tendon
 rehabilitation 812–13
 Flint, Austin 18–20
 fludrocortisone, septic shock 669
 fluid resuscitation of sick children in Africa 532–3
 fluoroquinolone resistance 246
 fluorouracil
 breast cancer 578–9, 583
 colorectal cancer 636–7
 gastro-oesophageal cancer 620–1
 glaucoma 743
 oesophageal cancer 618–19
 pancreatic cancer 630–1
 fluticasone
 atopic eczema 105
 chronic obstructive pulmonary disease 462–3
 rhinosinusitis with nasal polypsis 785
 foam scleropathy (FS), varicose veins 920–1
 folic acid, pancreatic cancer 630–1
 follow-up, and quality assessment 43
 fondaparinux, non-ST elevation acute coronary syndrome 68–9, 73
 Foo, I 808–9
 Forbes, John 17, 566–7
 Ford, A 212–13
 Forman, D 212–13
 formoterol
 asthma 455
 chronic obstructive pulmonary disease 460
 Forrest, Sir Patrick 560
 Foss, N 162–3
 Fossard, D 472–3
 foxglove 6, 10, 56
 Frederiksen, J 370–1
 FREEDOM 82–3
 Frisell, J 572–3
 Fröbert, O 66–7
 Frost, H 696–7
 Fuchs, B 666–7
 fundoplication, gastro-oesophageal reflux disease
 laparoscopic vs medical management 614–15
 laparoscopic vs open 616–17
 FUTURE II 250–1
- G**
 gabapentin (GBP)
 new-onset epilepsy 282–3
 partial-onset epilepsy 362–3
 peripheral neuropathy 382–3
 Gaede, P 146–7
 GALA 904–5
 Galen 6, 560
 Gallo, JJ 396–7
 gallstone pancreatitis, acute 626–7
 Galmiche, J 614–15
 Galton, Francis 19–20
 ganciclovir, cytomegalovirus infection 836–7
 congenital 526–7
 Garbuz, D 850–1
 Garrod, AB 486
 Gaskin, G 444–5
 gastric cancer
 D1 vs D2 resection 622–3
 Helicobacter pylori eradication 210–11
 gastric ulcer 212–13
 gastroenterology 205–39
 gastrointestinal bleeding see upper gastrointestinal bleeding
 gastrointestinal surgery 611–47
 gastro-oesophageal cancer 620–1
 gastro-oesophageal reflux disease (GORD)
 medical vs surgical management 614–15
 type of surgery 616–17
 Gates, S 168–9
 gauze therapy vs vacuum-assisted closure 806–7
 Gavarret, L 12
 Ge, D 344–5
 Geddes, J 392–3
 gefitinib, non-small cell lung cancer 483
 Gejjo, P 340–1
 Gelber, R 524–5
 gemcitabine
 non-small cell lung cancer 480, 481
 pancreatic cancer 630–1
 generalizing evidence to your patient 50–1
 GENEVA Study Group 758–9
 genital herpes
 antiviral therapy 254–5
 prevention of outbreaks 256–7
 genital warts 252–3
 genitourinary medicine 241–61
 George I 9
 geriatric medicine 263–85
 see also older people
 Gerslick, AH 64–5
 Gerstein, H 136–7
 Ghanem, K 244–5
 Gibbon, John Heysham 592
 Gilbert, R 520–1
 Giles, M 354–5
 Gillespie, B 742–3
 GIMEMA 302–3
 Gines, A 230–1
 Girard, T 666–7
 Girvin, JP 704–5
 GISEN Group 434–5
 Glasziou, P 770–1
 glatiramer acetate, multiple sclerosis 373
 glaucoma 738
 early treatment 746–7
 intraocular pressure control 740–1, 744–5
 early treatment 746–7
 medical vs surgical treatment 742–3
 topical medication 744–5
 gliomas, low-grade (LGGs) 694–5
 Glogovac, S 812–13
 glomerulonephritis 436–7

- glucagon-like peptide-1 (GLP-1) analogues, diabetes mellitus 142–3
- glucocorticoids, alcoholic hepatitis 228–9
- glucose control, diabetes mellitus 134–5
- glucose lowering, diabetes mellitus 136–7
- glycaemic control in critically ill patients 658–9
- glycaemic memory 134
- Goddijn, M 716–17
- Godlee, Sir Rickman 674
- Godwin, J 578–9
- Goekoop-Ruiterman, Y 494–5
- Gohel, MS 922–3
- goitre 184–5
- Gold, H 18–19
- Goldacre, Ben 27–8
- Goldsmith, K 416–17
- Goldstein, I 876–7
- Goldstein, P 64–5
- Goldthwait, Joel E 486
- Gomis, T 130–1
- gonorrhoea
antibiotic resistance 246–7
tests 242
- Goodacre, S 174–5
- Goodman, P 886–7
- Gordon, S 236–7
- goserelin, prostate cancer 889
- gout 486
NSAIDs and COX-2 inhibitors 502–3
- GRADE
applying evidence to your patient 51
quality of evidence 38–9, 39
- graded exercise therapy (GET) 416–17
- Grading of Recommendations, Assessment, Development and Evaluation see GRADE
- Grange, J 224–5
- Granger, CB 76–7, 90–1
- GRASP 246–7
- Graves' disease 182–3
- Gray, A 174–5
- great saphenous varicose veins 920–1
- Greeffhorst, A 460–1
- Green, BL 634–5
- Greening, A 454–5
- Greenwell, T 878–9
- Greenwood, Major 19–20, 22
- Gregson, BA 680–1
- Griffiths, T 458–9
- groin hernia repair 644–5
- grommets in otitis media with effusion 772–5
- gross total resection (GTR), low-grade gliomas 694–5
- Grubb, RL 686–7
- Grundman, M 274–5
- Gruntzig, Andreas 898
- guidelines for clinical practice 50–1
- Guilhot, F 298–9
- Guillain-Barré syndrome (GBS) 380–1
- Gull, Withey 18–20
- Guner, F 252–3
- Gurfinkel, E 72–3
- Guyatt, G 862–3
- gynaecology 707–35
- H**
- Haahtela, T 450–1
- Habr-Gama, A 642–3
- Haider, R 540–1
- haemangiomas, infantile 102
- haematology 287–311
- haematuria assessment in bladder cancer 892–3
- Hajenius, P 712–13
- Hall, A 540–1
- Haller, J 758–9
- Halliday, A 900–1
- Halsted, William Stewart 560
- Hammond, P 130–1
- Hanaway, MJ 824–5
- Hankins, G 718–19
- Hanlon, T 402–3
- Hannah, M 724–5, 726–7
- Hannah, W 726–7
- Harden, M 520–1
- Harrell, SP 792–3
- Harrison, E 900–1
- Hatlebakk, J 614–15
- Hauschild, A 124–5
- Havir, D 326–7
- Havstad, S 172–3
- Haygarth, John 17
- Haynes, A 544–5
- Hayter, E 900–1
- hazard ratio (HR) 48
- head injury
corticosteroids 676–7
paediatric 156–7
phenytoin prophylaxis 678–9
- Heald, R 638–9
- heart failure (HF)
angiotensin II receptor antagonists 90–1
 β -blockers 86–7
cardiac resynchronization therapy 94–5
implantable cardioverter-defibrillator vs amiodarone 92–3
revascularization 96–7
spironolactone 88–9
- heart
transplantation 816–17
- Hebert, P 290–1
- Hedayati, M 184–5
- HEDS-APT 762–3
- HEDS-EKT 763
- HEDS-RFS 763
- Heijl, A 746–7
- Heinrichs, D 402–3
- Helicobacter pylori*
gastric cancer 210–11
peptic ulcer disease 206, 212–13
- Hellstrom-Lindberg, E 306–7
- Helsinki Declaration 26–7
- hemiarthroplasty, hip fracture 846–7
- heparin see low-molecular-weight heparin; unfractionated heparin
- hepatitis, alcoholic see alcoholic hepatitis
- hepatitis C
chronic, triple therapy in 238–9
in HIV-positive individuals 324–5
liver transplantation 834–5
- peginterferon and ribavirin 236–7
- predictors of response 344–5
- hepatobiliary surgery 611–47
- hepatology 206
- HERA 586–7
- herceptin, breast cancer 586–7
- Herkowitz, HN 698–9
- hernia repair 644–5
- herpes
genital see genital herpes
ocular 762–3
- Herpetic Eye Disease Study Group 762–3
- Herrala, J 450–1
- Heuer, D 744–5
- Heule, F 806–7
- Hewson, S 726–7
- Heydendaal, V 112–13
- hidradenitis suppurativa 102

- Higginbotham, E 744–5
 high-frequency oscillation (HFO) for acute respiratory distress syndrome 660–1
 highly active antiretroviral therapy (HAART) 314
 Hill, Austin Bradford 4, 19–20, 22
 hip arthroplasty 850–1
 hip fracture
 delirium following 272–3
 dynamic hip screw 844–5
 fascia iliaca block after 162–3
 hemiarthroplasty vs internal fixation 846–7
 hormone replacement therapy 729
 hip replacement, total 866–7
 hip screw, dynamic 844–5
 Hippocrates 11, 840
 humoralism 486
 histamine (H₂) receptor blockers, stress ulcer prophylaxis 664–5
 history of evidence-based medicine 3–31
 HIV 242, 313–27
 antiretroviral therapy 314
 continuous vs intermittent 318–19
 in HIV-associated TB 326–7
 new agents for treatment-experienced individuals 320–1
 to prevent HIV transmission 316–17
 ritonavir-boosted atazanavir vs efavirenz and comparison of two NRTI backbones 322–3
 combination treatment for hepatitis 324–5
 maternal-infant transmission 524–5
 tuberculous meningitis 332, 333
 Hobbs, F 266–7
 Holdgate, A 880–1
 Holen, K 842–3
 Holley, R 258–9
 Hollingsworth, K 144–5
 Hollmann, M 646–7
 Holman, R 134–5
 Holmberg, L 890–1
 homeopathy 17
 Honigfeld, G 404–5
 Hoogma, R 130–1
 Hooper, R 268–9
 Hopkinson, Z 730–1
 hormone replacement therapy (HRT) 728–9
 Horsley, Sir Victor 674
 Hortobagyi, G 588–9
 Houeto, JL 702–3
 Howman, A 436–7
 HPTN 052 316–17
 Hudson, A 830–1
 Huhtala, H 182–3
 human immunodeficiency virus see HIV
 human leucocyte antigen (HLA)-incompatible kidney recipients 828–9
 human papillomavirus vaccine (HPV) 250–1
 Humar, A 836–7
 humoralism 486
 Hung, L 214–15
 Hurwitz, H 636–7
 Hussein, M 746–7
 Hutson, R 200–1
 Hutton, J 166–7
 hydrocortisone, septic shock 668–9
 hydroxyapatite (HA)-coated Schanz pins 860–1
 hydroxychloroquine, rheumatoid arthritis 494–5
 hyperparathyroidism, primary
 medical treatment 188–9
 surgical treatment 190–1
 hyperprolactinaemia 202–3
 hypertension (HTN) 60–1
 ocular (OHT) 744–5
 hyperthyroidism
 methimazole 184–5
 radioiodine 182–3, 184–5
 hypertrophic burn scars 804–5
 hypogonadism, male 196–7
 hypothermia
 cardiac arrest 170–1, 670–1
 perinatal asphyxial encephalopathy 516–17
 Hypothermia After Cardiac Arrest Study Group 670–1
 hypothyroidism 186–7
- ifosfamide, non-small cell lung cancer 480
 Illingworth, R 682–3
 imatinib, chronic myeloid leukaemia 298–9
 imiquimod, genital warts 252–3
 immune reconstitution inflammatory syndrome (IRIS) 326–7
 immunomodulator cream, genital warts 252–3
 immunosuppression
 membranous nephropathy 436–7
 transplantation 816–17
 kidney 820–7
 liver 834–5
 IMPACT 556–7
 implantable cardioverter-defibrillator (ICD) 92–3
 importance of study data, assessment of 44
 Ind, P 454–5
 Independent UK Panel on Breast Cancer Screening 562–3
 indometacin, gout 502–3
 infectious diseases 329–45
 infertility treatment 732–3
 inflammatory bowel disease 206
 infliximab
 ankylosing spondylitis 500–1
 Crohn's disease 234–5
 psoriasis 114–15
 rheumatoid arthritis 492–5
 inguinal hernia repair 644–5
 insulin
 type 1 diabetes mellitus 130–1
 type 2 diabetes mellitus
 coronary artery disease 80–1
 intensive glucose control 134, 135
 INTAC 824–5
 intensive care 649–71
 intention-to-treat analysis 43
 INTEREST 483
 interferon (IFN)
 chronic myeloid leukaemia 298–9
 hepatitis 236–7
 multiple sclerosis 372–3
 pegylated see pegylated interferon
 randomized controlled trials 23–4

internal mammary artery (IMA) graft 602
 International Society of Nephrology 420
 interpersonal psychotherapy (IPT), bulimia nervosa 410–11
 intracerebral haemorrhage, early surgery for 680–1
 intracranial aneurysms, ruptured 684–5
 intraocular pressure (IOP) control, glaucoma 740–1, 744–5
 early treatment 746–7
 intravenous
 immunoglobulin (IVIG) Guillain-Barré syndrome 380–1
 Kawasaki disease 528, 529
 intravenous pyelogram (IVP) 892–3
 Ioannidis, J 580–1
 ipratropium, chronic obstructive pulmonary disease 460–1, 466
 irinotecan, colorectal cancer 636–7
 IRIS 298–9
 ISAT 684–5
 ischaemic stroke 352–3
 Isenmann, R 628–9
 islet cell transplantation 132–3
 isoniazid, tuberculous meningitis 332
 isotretinoin, acne 102, 118–19
 IST-3 352–3
 Iye, P 326–7

J

Jaatinen, P 182–3
 Jackson, Hughlings 674
 Jacobson, I 238–9
 Jacoby, A 358–9
 Jaeschke, R 664–5
 Jager, J 490–1
 Jahr, JS 552–3
 Jakola, AS 694–5
 JAMA, quality assessment checklist for RCTs 42
 James, D 626–7
 Jamrozik, K 550–1
 Jansen, E 604–5
 Jayne, D 444–5
 Jenkinson, C 476–7
 Jenner, Edward 6
 Johnson, A 358–9, 416–17
 Johnson, K 848–9
 Johnson, P 872–3

Johnson, RJ 830–1
 Johnsson, F 616–17
 Johnstone, E 394–5
 Joint Consensus Statement on the Initial Assessment of Haematuria 892
 Joly, P 120–1
 Jones, R 410–11
 Jorenby, D 470–1
 Journal of the American Medical Association (JAMA), quality assessment checklist for RCTs 42
 Judkins, MP 898
 Juszcak, E 280–1

K

Kaandorp, SP 716–17
 Kakkar, V 472–3
 Kalra, L 350–1
 Kane, J 404–5
 Kappetein, AP 84–5, 600–1
 Karpf, D 192–3
 Karvonen, A 522–3
 Kass, M 744–5
 Katon, W 396
 Katz, J 856–7
 Kavanaugh, A 488–9
 Kawasaki disease 528–9
 Kehlet, H 554–5
 Kelman, Charles 738
 Kendall, J 158–9
 Kendall, M 326–7
 Kenyon, S 722–3
 Kerr, RS 684–5
 ketamine for procedural sedation 161
 ketofol for procedural sedation 161
 Key, D 668–9
 Khac, E 224–5
 Khadra, M 892–3
 Khan, R 846–7
 kidney disease, chronic (CKD)
 erythropoietin-stimulating agents and cardiovascular risk 426–7
 protein restriction and blood pressure control 424–5
 statins, ezetimibe, and cardiovascular risk 428–9
 kidney injury, acute 422–3
 kidney transplantation 420
 deceased donors 830–1
 kidney
 preservation 818–19
 desensitization 828–9
 developments 816–17
 immunosuppression belatacept 820–1

induction 824–5
 maintenance 822–3, 826–7
 preservation 818–19
 skin cancer 826–7
 Kiguli, S 532–3
 Kimball, A 116–17
 Kimberlin, D 526–7
 kinematic assessment 840
 King, K 828–9
 Kiss, D 642–3
 Kjekshus, J 58–9
 Klahr, S 424–5
 Klareskog, L 490–1
 Klassen, P 188–9
 Klintmalm, GB 834–5
 Kloster, R 694–5
 knee injuries, magnetic resonance imaging 852–3
 knee replacement
 total 866–7
 unicompartmental (UKR) 858–9
 Kobayashi, T 528–9
 Kodali, S 608–9
 Koes, B 506–7
 Kolb, E 154–5
 Koller, MT 154–5
 Koopman, J 792–3
 Korczyn, A 374–5
 Korttila, K 556–7
 Kosorok, M 518–19
 Kralj-Hans, I 208–9
 Krekels, G 802–3
 Kress, J 666–7
 Kristensen, B 162–3
 Kron, M 628–9
 Kumar, M 222–3
 Kyungmann, K 478–9

L

labour
 induction 724–5
 spontaneous preterm (SPL) 722–3
 Lacomblez, L 378–9
 Laennec, René 12–13
 Lagerqvist, B 66–7
 Lahdensuo, A 450–1
 Lakey, J 132–3
 Lakhnampaul, M 530–1
 Lam, S 210–11
 Lamb, S 166–7, 168–9, 660–1
 Lamba, G 222–3
 Lambert, PC 530–1
 lamivudine, HIV 322–3
 lamotrigine (LTG)
 generalized and unclassified epilepsy 364–5
 new-onset epilepsy 282–3
 partial-onset epilepsy 362–3

- Lancaster, Sir Captain James 8
- Langdon, MM 436–7
- lanreotide, acromegaly 199
- Larson, R 298–9
- Larsson, S 616–17
- laryngopharyngeal reflux (LPR) 792–3
- laryngoscopy, and use of cricoid pressure 546–7
- laser-assisted *in situ* keratomileusis (LASIK) 760–1
- laser photocoagulation, diabetic retinopathy 752–3
- macular oedema 754–5
- laser treatment
- diabetic retinopathy 756–7
 - photocoagulation see laser photocoagulation
- LASIK 760–1
- LATTE 584–5
- Latter, V 158–9
- Lau, J 220–1
- Lawaetz, M 920–1
- Lawler, P 394–5
- Laxova, A 518–19
- Le Carré, John, *The constant gardener* 27
- LEAD-6 142–3
- Lebrun-Vignes, B 256–7
- Lee, AYY 308–9
- Lee, C 552–3
- Lee, KL 92–3, 96–7
- Leeflant, MM 106–7
- leflunomide, rheumatoid arthritis 494–5
- left main stem disease 600–1
- Legro, R 732–3
- Leischow, S 470–1
- Leonardi, C 116–17
- Lepage, E 300–1
- Leske, M 746–7
- Leslie, K 548–9
- leucovorin, colorectal cancer 636–7
- leukotriene receptor antagonists, asthma 456–7
- Leung, W 220–1
- levels of evidence 39
- levetiracetam
- generalized and unclassified epilepsy 365
 - partial-onset epilepsy 363
- Levey, A 424–5
- Levine, MN 308–9
- levodopa, Parkinson's disease 374–7
- levothyroxine, hypothyroidism 186–7
- Levy, M 662–3
- Lewis, Sinclair, *Arrowsmith* 26
- Leyland-Jones, B 586–7
- Leys, D 908–9
- Li Wan Po, A 110–11
- Lichter, P 742–3
- Liddle, A 858–9
- Lidwell, O 866–7
- Lieberman, JA 400–1
- likelihood ratio (LR) 49
- Lillehei, C. Walton 592
- Lim, E 144–5
- Lin, C-Y 526–7
- Lind, James 23, 4, 8
- Lindskog, D 844–5
- linear salpingostomy 710–11
- Linn-Rasker, S 186–7
- liraglutide, diabetes mellitus 142–3
- Lister, Joseph 14, 674
- Listing, J 500–1
- lithium therapy, discontinuation in bipolar disorder 398–9
- lithotripter, extracorporeal 870
- Litière, S 576–7
- Little, Rod 150
- Liu, C 624–5
- Liu, M 832–3
- liver transplantation 834–5
- Lo, C 624–5
- Lo-Coco, F 304–5
- Loewi, Otto 180
- Lomas, JP 156–7
- London, N 626–7
- long-acting β_2 agonists (LABAs)
- asthma 454–5
 - chronic obstructive pulmonary disease 462–3
- long bones, external fixation of 860–1
- long-term oxygen therapy (LTOT), chronic obstructive pulmonary disease 464–5
- Lonze, B 828–9
- Loop, F 602–3
- LOTUS 614–15
- Louis, Pierre 11, 12
- low-molecular-weight heparin (LMWH)
- miscarriage, recurrent antiphospholipid antibodies 714–15
 - unexplained 716–17
- myeloma 303
- non-ST elevation ACS 72, 73
- pulmonary embolism 472–3
- comparison with UFH 474–5
- venous thromboembolism 310–11
- in cancer 308–9
- Lowbury, E 866–7
- lower back pain, surgery for 696–7
- lower limb ischaemia 898
- Lower pole 1 884–5
- Lower pole 2 885
- Lue, T 876–7
- lumbar disc herniation, surgery for 700–1
- lumbar spine pain, surgery for 696–7
- Lumsden, M 734–5
- Lund-Andersen, H 146–7
- Lundgren, J 318–19
- lung cancer
- non-small cell chemotherapy 480–1
 - epidermal growth factor receptor inhibitors 482–3
 - small cell 478–9
 - and smoking 448
- lung transplantation 832–3
- lung volume reduction surgery (LVRS) 468–9
- lupus nephritis (LN)
- induction with mycophenolate mofetil vs cyclophosphamide 438–9
 - maintenance with mycophenolate mofetil vs azathioprine 440–1
- Lurie, JD 700–1
- luteinizing hormone-releasing hormone (LHRH) analogues, prostate cancer 888–9
- Lyles, K 194–5
- Lyman, J 854–5
- Lyme disease 342–3
- lymphadenectomy
- gastric cancer 622–3
 - melanoma 800–1
- lymphoblastic leukaemia, acute (ALL) 296–7
- lymphoma, diffuse large B-cell 300–1
- Lytle, B 602–3

M

- Maathuis, MJ 818–19
- McCauley, M 316–17
- McConnell, J 874–5
- McEvoy, JP 400–1
- MacEwen, Sir William 674
- MacFarlane, J 638–9

- McGale, P 574–5
 McHutchison, J 236–7, 238–9
 Mackay, D 810–11
 Mackay, M 698–9
 McNeil, J 548–9
 McNicholas, T 196–7
 McNutt, R 50
 macular oedema
 diabetic retinopathy
 laser and vascular endothelial growth factor antagonists 756–7
 laser photocoagulation 754–5
 retinal vein occlusion 758–9
 Macular Photocoagulation Study Group 748–9
 MAGIC 620–1
 Maglio, C 140–1
 magnesium sulfate, pre-eclampsia 720–1
 magnetic resonance imaging (MRI), knee injuries 852–3
 MAGPIE 720–1
 Maini, R 492–3
 Maitland, K 532–3
 malaria 330, 334–7
 male hypogonadism 196–7
 malignant melanoma, excision margins 798–9
 Mallolas, J 324–5
 Maltête, D 702–3
 mammoplasty
 augmentation 808–9
 reduction 810–11
 Mangioni, C 260–1
 Manns, M 236–7
 Mant, J 266–7
 Mantese, VA 906–7
 Marangoni, F 292–3
 maraviroc, HIV 320
 Marcantonio, E 272–3
 Marcus, CL 788–9
 Marek, DA 96–7
 Margallo-Lana, M 280–1
 Mark, DB 92–3
 Marks, J 108–9
 Marmo, R 216–17
 Marsh, J 166–7
 Marshall, HC 634–5
 Marson, A 358–9
 Martin, DH 248–9
 Martin, M 260–1
 Mas, JL 908–9
 Mason, WP 692–3
 Masri, B 850–1
 MASS 910–11
 mastectomy 560
 vs breast-conserving surgery 568–9
 MASTER 550–1
 Mathurin, P 226–7
 Mauri, D 580–1
 maxillomandibular advancement (MMA), obstructive sleep apnoea 790–1
 MDRD 424–5
 mechanical heart valve vs biological valve 606–7
 mechanical ventilation, sedation and ventilator weaning protocol 666–7
 MEDAL 498–9
 Medical Research Council (MRC)
 Antiepileptic Drug Withdrawal Trial 360–1
 chronic obstructive pulmonary disease 464–5
 CLASICC 634–5
 gastric cancer, D1 vs D2 resection 622–3
 haematology 288
 Laparoscopic Groin Hernia Trial Group 644–5
 Multicentre Otitis Media Study Group 774–5
 Oesophageal Cancer Working Group 618–19
 prostate cancer 890
 rectal cancer and neoadjuvant radiotherapy (MRC CR07) 640–1
 trauma unit 150
 tuberculosis 22, 330
 medicine tradition 6
 Medline 40–1
 Mehta, SR 68–9, 76–7
 Meininger, V 378–9
 melanoma
 excision margins 798–9
 lymph node status 800–1
 metastatic see metastatic melanoma
 melphalan, myeloma 302–3
 Meltzer, H 404–5
 memantine, Alzheimer's disease 278–9
 membranous nephropathy 436–7
 Mendelow, AD 680–1
 Mendenhall, L 226–7
 meningitis, tuberculous 330, 332–3
 meniscal tear and osteoarthritis 856–7
 MEPEX 444–5
 mepivacaine after hip fracture 162
 Merenstein, D 780–1
 Mesmer, Franz Anton 16–17
 mesmerism 16–17
 mesorectal excision, total, in rectal cancer 638–9
 neoadjuvant radiotherapy 640–1
 MESS 358–9
 metastatic melanoma 102
 BRAF inhibitors 124–5
 metformin
 polycystic ovary syndrome 730–1
 infertility treatment 732–3
 type 2 diabetes mellitus 134, 135
 methimazole, hyperthyroidism 184–5
 methylprednisolone, multiple sclerosis 370–1
 methodology, and quality assessment 43
 methotrexate (MTX) 102
 atopic eczema 106–7
 breast cancer 578–9
 psoriasis 112–13, 115
 rheumatoid arthritis 488–95
 B-cell-targeted therapy 496, 497
 tubal ectopic pregnancy 712–13
 methylphenidate, ADHD 414–15
 methylprednisolone
 alcoholic hepatitis 226
 atopic eczema 105
 head injury 676–7
 Kawasaki disease 528
 renal vasculitis 444–5
 methylxanthines, apnoea of prematurity and cerebral palsy 514–15
 metoprolol
 heart failure 87
 myocardial infarction 62–3
 metronidazole
 bacterial vaginosis 260–1
 pancreatitis, acute 628, 629
 Metso, S 182–3
 microscopic polyangiitis 444
 mid-shaft clavicle fractures 864–5
 midazolam for procedural sedation 160–1
 MIGR-001 366–7
 migraine
 prophylaxis 366–7
 sumatriptan 368–9

- mild cognitive impairment (MCI), preventing progression of 274–5
- Miller, G 882–3
- Miller, M 136–7
- Miller, P 194–5
- Milwaukee Academy of Medicine 17
- mINT 168–9
- miscarriage, recurrent
- antiphospholipid antibodies 714–15
 - unexplained 716–17
- mitomycin
- bladder cancer 894–5
 - non-small cell lung cancer 480
- mitral valve replacement (MVR) 606–7
- Moers, C 818–19
- Mohr, FW 84–5, 600–1
- Mohs' micrographic surgery (MMS) 802–3
- Mol, B 712–13
- Molyneux, AJ 684–5
- Monesillo, A 230–1
- Montagu, Lady Mary 9
- montelukast, asthma 456–7
- Montgomery, R 828–9
- Montini, M 198–9
- Moore, RH 788–9
- Moore, W 546–7
- Morales, KH 396–7
- Morello, E 826–7
- Morice, M-C 84–5, 600–1
- morphine
- analgesia in
 - children 158, 159 - after hip fracture 162, 163
- Morton, D 800–1
- Moss, J 734–5
- Moss, S 632–3
- motor neuron
- disease 378–9
- Mouës, C 806–7
- MPS 748–9
- Mroczkowski, TF 248–9
- MSLT 800–1
- MTA Cooperative Group 414–15
- MTOPS 874–5
- Mufti, G 306–7
- Muhr, G 860–1
- Mulder, H 196–7
- Mulgaonkar, S 824–5
- Muller, I 778–9
- Mullins, R 476–7
- multinodular goitre (MNG) 182–3
- multiple sclerosis (MS) 348
- beta-interferon 372–3
 - corticosteroids 370–1
- multivessel coronary artery disease
- PCI vs CABG 84–5
- surgery
- vs angioplasty 596, 597
 - vs bare-metal stent 598–9
 - vs drug-eluting stent 600–1
- Muqford, M 656–7
- Murray, D 858–9
- Murray, GD 682–3
- Murray, George 180
- Musch, D 742–3
- mycophenolate mofetil (MMF)
- lupus nephritis
 - induction therapy 438–9
 - maintenance therapy 440–1
 - transplantation
 - kidney 823
 - liver 834, 835
- myelodysplasia 306–7
- myeloid leukaemia
- acute (AML) 292–3
 - chronic (CML) 298–9
- myeloma 302–3
- Myeloma XI 303
- Myles, P 548–9, 550–1
- myocardial infarction
- clopidogrel and metoprolol 62–3
 - pre-hospital thrombolysis
 - vs primary percutaneous intervention 64–5 - thrombus aspiration 66–7
- myopia 738, 760–1
- Myrmel, KS 694–5
- N**
- N-acetylcysteine, alcoholic hepatitis (NAC) 228–9
- nadroparin, unexplained recurrent miscarriage 716
- nalidixic acid resistance 338
- naproxen, and cardiovascular risk 499
- nasal continuous positive airways pressure (nCPAP), obstructive sleep apnoea 476–7
- nasal polyposis 784–5
- NASCET 902–3
- NASCIS II and III 677
- natalizumab, multiple sclerosis 373
- National Cancer Institute of Canada Clinical Trials Group 482–3
- National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group 526–7
- National Institute of Child Health and Human Development (NICHD) 516, 517
- National Institute of Neurological Disorders 352–3
- National Surgical Adjuvant Breast and Bowel Project P-1 Study 564–5
- National Surgical and Adjuvant Breast Project (NSABP) 560
- nausea,
- post-operative 556–7
- NCIC-CTG C016 640–1
- Neaton, J 318–19
- neck of femur fracture see hip fracture
- Needham, D 654–5
- negative predictive value (NPV) 49
- neomycin, otitis externa 768–9
- neonates, developmental dysplasia of the hip 842–3
- Neoptolemos, J 626–7, 630–1
- nephrolithiasis 884–5
- nephrolithotomy, percutaneous (PCNL) 884–5
- nephrology see renal medicine
- nephropathy
- membranous 436–7
 - non-diabetic 434–5
- nephrostomy,
- percutaneous 882–3
- Ness, R 258–9
- Nestle, F 114–15
- Neto, W 366–7
- NETT 468–9
- Nettleton, Thomas 9
- neurology 347–85
- neuromuscular blockade 552–3
- neuropathy,
- peripheral 382–3
- neurosurgery 673–05
- Newby, D 174–5
- Newton, Isaac 6
- NEXUS 153
- Nguyen, B 172–3
- Nguyen-Khac, E 228–9
- NICE-SUGAR 658–9
- Nichols, Edward H 486
- nicotine replacement therapy (NRT) 470–1

Nides, M 470–1
 Nielsen, P 370–1
 Nierich, A 604–5
 nilotinib, chronic myeloid leukaemia 299
 Nilsson, G 616–17
 nimodipine, subarachnoid haemorrhage 682–3
 nitinol stents 918–19
 nitrogen carrier, post-operative nausea and vomiting 556, 557
 Noman, M 232–3
 non-diabetic nephropathy 434–5
 non-invasive positive pressure ventilation (NIPPV) 174–5
 non-invasive ventilation (NIV)
 acute cardiogenic pulmonary oedema 174–5
 chronic obstructive pulmonary disease 466–7
 see also continuous positive airways pressure;
 non-invasive positive pressure ventilation
 non-ST elevation acute coronary syndrome
 clopidogrel 74–5
 enoxaparin 72–3
 fondaparinux 68–9
 ticagrelor 70–1
 timing of intervention 76–7
 non-steroidal anti-inflammatory drugs (NSAIDs)
 gout 502–3
 renal colic 880–1
 norepinephrine, septic shock 652–3
 Northfield, M 454–5
 Northwick Park electroconvulsive therapy trial 394–5
 NOTT US 465
 novel oral anticoagulants (NOACs)
 venous thromboembolism 311
 Novotny, W 636–7
 Nowakowski, J 342–3
 null hypothesis 43
 number needed to harm (NNH) 48
 number needed to treat (NNT) 47–8
 numerical method 11
 Nunn, AJ 122–3
 Nuremberg Code 26–7

O

O'Brien, D 160–1
 O'Brien, S 298–9
 O'Rourke, R 78–9
 OASIS 5 68–9
 obstetrics 707–35
 obstructive
 pyelonephritis 882–3
 obstructive sleep apnoea (OSA)
 childhood 788–9
 nasal continuous positive airway pressure 476–7
 surgery vs positive airway pressure 790–1
 Octopus trial 604–5
 octreotide,
 acromegaly 198–9
 ocular herpes simplex 762–3
 ocular hypertension (OHT) 744–5
 odds ratio (OR) 48
 Oehrborg, S 408–9
 oesophageal cancer 618–19
 ofloxacin, enteric fever 338–9
 Ohlsson, A 724–5
 OHTS 744–5
 olanzapine
 dementia 281
 schizophrenia 400, 401
 Older, P 540–1
 older people
 cardiopulmonary exercise testing, preoperative 540–1
 hip fracture 846–7
 see also geriatric medicine
 Olivecrona, GK 66–7
 Oliver, George 180
 Olsen, T 118–19
 omeprazole
 gastro-oesophageal reflux disease 614
 laryngopharyngeal reflux 793
 upper gastrointestinal bleeding 220–1
 oncotype DX 579
 ondansetron, post-operative nausea and vomiting 556, 557
 Oosterlinck, W 894–5
 ophthalmology 737–63
 opioids, renal colic 880–1
 Opmeer, B 112–13
 Opoka, R 532–3
 ORACLE 722–3
 orthopaedics 839–67
 OSCAR 660–1

OSCILLATE 660, 661
 osteoarthritis (OA) 486
 cardiovascular outcomes with drug therapies 498–9
 partial meniscectomy 856–7
 osteoporosis,
 post-menopausal 192–3
 Osterag, G 802–3
 Otani, T 528–9
 otitis externa 768–9
 otitis media
 acute (AOM) 770–1
 with effusion (OME) adjuvant adenoidectomy 774–5
 grommets 772–5
 otorhinolaryngology 765–93
 Ottawa ankle rules 154–5
 outcome and exposure table 46
 Owen, J 466–7, 718–19
 oxaliplatin, gastro-oesophageal cancer 621
 oxcarbazepine, partial-onset epilepsy 362–3
 Oxenham, H 606–7
 Oxford Vascular Study (OXVASC) 354
 oxygen therapy, chronic obstructive pulmonary disease 464–5
 oxytetracycline, syphilis 244
 oxytocin, prelabour rupture of membranes 724–5

P

p-values 48
 Paavonen, J 260–1
 PACE 416–17
 packed red cell transfusion threshold 290–1
 paclitaxel, coronary artery disease
 in diabetes 83
 multivessel disease 84–5
 Padma-Nathan, H 876–7
 paediatrics 511–33
 head injury, CT scanning in 156–7
 nasal diamorphine for analgesia 158–9
 neonatal developmental dysplasia of the hip 842–3
 obstructive sleep apnoea 788–9
 otitis media
 acute 770–1
 with effusion 772–3

- paediatrics (*Contd.*)
 sore throat, acute 786–7
 stroke prevention in sickle-cell disease 294–5
 upper respiratory tract infections, recurrent 782–3
- Paganelli, G 570–1
- Paget, Stephen 592
- Paget's disease 194–5
- painful shoulder syndrome 506–7
- Palumbo, A 302–3
- pamidronate, breast cancer 588–9
- pancreatic cancer 630–1
- pancreatitis
 acute 628–9
 acute gallstone 626–7
- Pandit, H 858–9
- panic disorder
 cognitive therapy 406–7
 pharmacological and psychological treatment 408–9
- Panicker, J 530–1
- pantoprazole, laryngopharyngeal reflux 792–3
- Papp, K 114–15, 116–17
- Pappworth, MH 26–7
- Paracelsus 6
- paracentesis, fluid replacement following 230–1
- parathyroidectomy 190–1
- Paré, Ambrose 7
- Parker, M 846–7
- Parkinson's disease (PD) 348
 early treatment 374–5
 levodopa timing 376–7
 surgery 702–3
- Parkinson's Study Group 376–7
- Parodi, Nicholas 898
- paroxetine, panic disorder 408–9
- Parry, C 338–9
- PARTNER 608–9
- Parving, H 146–7
- Patchell, RA 688–9
- Patey, DH 560
- patient factors, applying evidence 50
- Paul, S 134–5
- Pauwels, R 452–3
- Pavlidis, N 580–1
- PCPT 886–7
- PEACH 258–9
- Peacock, M 188–9
- peak expiratory flow (PEF) monitoring, asthma 450–1
- Pearle, M 882–3
- Pearson, Karl 19–20
- PECARN rule 157
- Peck, G 118–19
- Pedersen, S 452–3
- Pedersen, T 58–9
- Pediatric AIDS Clinical Trials Group Protocol 076
- Study Group 524–5
- Peek, G 656–7
- pegvisomant, acromegaly 200–1
- pegylated interferon hepatitis 236–7, 238–9, 344–5
 in HIV-positive individuals 324–5
- pelvic inflammatory disease (PID) 258–9
- pemphigoid, bullous 120–1
- penicillin
 recurrent cellulitis 122–3
 sore throat, acute, in children 786–7
 syphilis 244–5
- peptic ulcer disease
 antiplatelet bleeding risk management 214–15
 endoscopic control of bleeding 216–17
Helicobacter pylori eradication 206, 212–13
- percutaneous
 intervention (PCI)
 coronary artery disease 78–9
 in diabetes 82–3
 multivessel disease 84–5
 myocardial infarction 64–5
 see also bare-metal stents; drug-eluting stents
- percutaneous nephrolithotomy (PCNL) 884–5
- percutaneous
 nephrostomy 882–3
- percutaneous transluminal angioplasty
 coronary artery disease 596–7, 598
 lower limb ischaemia 898
- Pereira, J 482–3
- Perel, P 542–3
- Perez, I 350–1
- Perez, R 642–3
- perindopril,
 hypertension 60–1
- peripheral arterial disease
 angioplasty vs stenting 918–19
 surgery vs angioplasty 916–17
- peripheral neuropathy 382–3
- perphenazine,
 schizophrenia 400, 401
- Petersen, R 274–5
- pethidine, renal colic 880–1
- Peto, R 578–9
- Petrarch 6–7
- Peveler, R 410–11
- Pfaffenrath, V 368–9
- Pfeffer, M 90–1
- phenytoin
 generalized and unclassified epilepsy 364
 new-onset epilepsy 282
 prophylactic 678–9
- Phillips, E 190–1
- PHOENIX 1 116–17
- photochemotherapy 108–9
- photocoagulation see laser photocoagulation, diabetic retinopathy
- photorefractive keratectomy (PRK) 760–1
- physic tradition in medicine 6
- physiotherapy
 meniscal tear and osteoarthritis 856–7
 shoulder pain 506–7
 whiplash 168–9
- Piccart-Gebhart, M 586–7
- Pichenot, M 320–1
- Pickard, JD 682–3
- Pickard, R 892–3
- PICO framework 36, 37
- Pierce, HL 882–3
- Pinczewski, L 854–5
- Piquet, M 228–9
- pirarubicin, bladder cancer 894
- Piscitelli, G 202–3
- Piscopo, R 216–17
- Pitt, B 88–9
- PIVOT 890
- placebos 16–17, 18–20
 as confounder 22
 ethics 18–19
- Plant, P 466–7
- plasma exchange (PE)
 Guillain-Barré syndrome 380–1
 renal vasculitis 444–5
- Plasma Exchange/
 Sandoglobulin Guillain-Barré Syndrome Trial Group 380–1
- plastic surgery 795–813
- platelet transfusion threshold 292–3
- PLATO 70–1
- pneumonia 11
- Pol, S 324–5
- Polli, A 202–3

Pollock, T 880–1
 polycystic kidney disease 442–3
 polycystic ovary syndrome (PCOS)
 infertility treatment 732–3
 metformin treatment 730–1
 polygeline following paracentesis 230–1
 polymyxin, otitis externa 768–9
 Pommer, A 860–1
 Porter, L 588–9
 positive airway pressure, obstructive sleep apnoea 790–1
 positive predictive value (PPV) 49
 post-operative nausea and vomiting (PONV) 556–7
 posterior canal benign paroxysmal positional vertigo (PC-BPPV) 776–7
 Powers, WJ 686–7
 pre-eclampsia 720–1
 PREDICT 875
 prednisolone (PSL)
 alcoholic hepatitis 226, 229
 asthma 450, 451, 454, 457
 Bell's palsy 384–5
 bullous pemphigoid 120, 121
 chronic obstructive pulmonary disease 460, 464, 466
 Kawasaki disease 528–9
 membranous nephropathy 436–7
 and methylprednisolone, equivalent doses 371
 myeloma 302–3
 renal vasculitis 444
 rheumatoid arthritis 494–5
 rhinosinusitis with nasal polyposis 784–5, 785
 virus-induced wheeze 530–1
 pregabalin 383
 prelabour rupture of membranes (PROM)
 management at term 724–5
 preterm see preterm, prelabour rupture of membranes
 prematurity
 apnoea of 514–15
 prevention by cervical cerclage 718–19

see also prelabour rupture of membranes;
 preterm, prelabour rupture of membranes
 PREMIER 488–9
 PREMODA 727
 Prentice R 728–9
 Present, D 234–5
 preterm birth see prematurity
 preterm, prelabour rupture of membranes (pPROM) 722–3
 Prieto-Merino, D 542–3
 PRISMS 372–3
 probenecid, pelvic inflammatory disease 259
 procedural sedation 160–1
 process of evidence-based medicine 36–41
 Procter, M 586–7
 PROfESS 356–7
 PROFET 268–9
 promyelocytic leukaemia, acute (APML) 304–5
 Pronovost, P 654–5
 Prontosil, puerperal fever 19–20
 propofol
 post-operative nausea and vomiting 556, 557
 procedural sedation 160–1
 propranolol
 infantile haemangiomas 102
 variceal bleeding 222–3
 PROSPECT 396–7
 prospective controlled trials 8
 prostaglandin, prelabour rupture of membranes 724–5
 prostate cancer
 hormone and radiotherapy 888–9
 prevention with finasteride 886–7
 radical prostatectomy 870
 vs active surveillance 890–1
 protein restriction, chronic kidney disease 424–5
 proton pump inhibitors (PPIs)
 laryngopharyngeal reflux 792–3
 stress ulcer prophylaxis 664–5
 upper gastrointestinal bleeding 220–1
 Prymula, R 522–3

psoralen ultraviolet A (PUVA), psoriasis 108–9
 psoriasis 102
 infliximab therapy 114–15
 methotrexate vs ciclosporin 112–13
 photochemotherapy vs dithranol 108–9
 topical calcipotriol 110–11
 ustekinumab therapy 116–17
 psychiatry 387–417
 PsychInfo 40
 Public Health England 246–7
 puerperal fever
 antiseptics 14
 Prontosil 19–20
 pulmonary embolism (PE)
 heparin type 474–5
 hormone replacement therapy 729
 post-operative prophylaxis 472–3
 pulmonary oedema, acute cardiogenic 174–5
 pulmonary rehabilitation 458–9
 pyelonephritis, obstructive 882–3
 pyrazinamide, tuberculous meningitis 332

Q

quality
 of evidence 39
 of RCTs, assessment 42–4
 QUEST 573
 Quetelet, Adolphe 12, 19–20
 quetiapine
 Alzheimer's disease 280–1
 schizophrenia 400
 quinine, falciparum malaria 330, 334–7

R

radical prostatectomy 870
 vs active surveillance 890–1
 radiofrequency ablation (RFA), varicose veins 920–1
 radioiodine, hyperthyroidism 182–3, 184–5
 radiostereometric analysis (RSA) 840
 radiosurgery for brain metastases 690–1

- radiotherapy (RT)
 astrocytoma, grade 4
 692–3
 breast cancer 560
 breast-conserving
 surgery 568–9, 574–5
 in situ cancer 576–7
 prostate cancer 888–9
 rectal cancer 638,
 639, 640–1
 long-course chemoradio-
 therapy 642–3
 small cell lung
 cancer 478–9
 spinal metastases 688–9
 whole-brain 690–1
- Radtke, A 776–7
- Rai, R 714–15
- RAISE 528–9
- RALES 88–9
- raltegravir, HIV 320
- Ramanathan, R 342–3
- ramipril, non-diabetic
 nephropathy 434–5
- Ramsay, R 282–3
- randomization
 first reference to 7
 quality assessment 43
- randomized controlled trials
 (RCTs) *xl*
 discontents 23–4
 first 22
 history of 4
 quality assessment 42–4
 rise 22–4
- ranibizumab
 age-related macular
 degeneration 748–51
 macular oedema 756–7
- Rao, DS 190–1
- Rascol, O 374–5
- Rasmussen, L 920–1
- Rasmussen, N 444–5
- Rebulla, P 292–3
- recombinant tissue
 plasminogen activator,
 ischaemic stroke 352–3
- reconstructive
 surgery 795–813
- rectal cancer
 long-course chemoradio-
 therapy 642–3
 neoadjuvant
 radiotherapy 640–1
 total mesorectal
 excision 638–41
- red cell transfusion
 threshold 290–1
 upper gastrointestinal
 bleeding 218–19
- Reeves, B 158–9
- Regine, WF 688–9
- Reich, K 114–15
- Reid, I 194–5
- REIN 434–5
- Reisberg, D 278–9
- Reiss, T 456–7
- relative risk (RR) 46
- relative risk reduction
 (RRR) 47
- remifentanyl, post-
 operative nausea and
 vomiting 556, 557
- Remme, W 88–9
- Renal Association 420
- renal calculi 884–5
- renal colic
 analgesia 880–1
 imaging 878–9
 obstructive pyelonephritis
 treatment 882–3
- renal failure, acute
 (ARF) 422–3
- renal medicine 419–45
- renal replacement therapy
 (RRT) 422–3
- renal transplantation *see*
 kidney transplantation
- renal vasculitis 444–5
- respiratory failure, severe
 adult 656–7
- respiratory
 medicine 447–83
- REST 734–5
- resuscitation of the sick
 child 532–3
- retinal vein occlusion 758–9
- retinoic acid, acute promye-
 locytic leukaemia 304–5
- retinoids 102
- acne 118–19
- revascularization
 coronary artery disease in
 diabetes 80–1
 heart failure 96–7
see also coronary artery
 bypass graft; percutane-
 ous intervention
- revision total hip arthro-
 plasty (THA) 850–1
- Rhazes 6–7
- rheumatic fever 10
- rheumatism 18–20
- rheumatoid arthritis
 (RA) 486
 B-cell-targeted therapy
 cardiovascular out-
 comes with drug
 therapies 498–9
 early treatment 494–5
 infliximab 492–3
 tumour necrosis factor- α
 antagonists 488–91
- rheumatology 485–507
- rhinosinusitis
 acute 780–1
 chronic, with nasal polypo-
 sis (CRSwNP) 784–5
- Rhodes, A 662–3
- ribavirin, hepatitis 236–7,
 238–9, 344–5
 in HIV-positive
 individuals 324–5
- Richardson, Frank L 486
- rifampicin
 brucellosis 340–1
 tuberculous meningitis 332
- Rigg, J 550–1
- Riley, Sir Harold 738
- riluzole, motor neuron
 disease 378–9
- risedronate, Paget's
 disease 194–5
- risperidone,
 schizophrenia 400
- Ritchie, P 160–1
- ritonavir, HIV 322–3
- rituximab
 diffuse large B-cell
 lymphoma 300–1
 membranous
 nephropathy 437
 rheumatoid
 arthritis 496–7
- rivaroxaban, venous throm-
 boembolism 310–11
- rivastigmine, Alzheimer's
 disease 280–1
- Rivers, E 172–3
- Robert, C 124–5
- Roberts, B 514–15
- Roberts, I 164–5, 542–3
- rocuronium, reversal by
 sugammadex 552–3
- Rodger, M 176–7
- Rodriguez-Zapata, M 340–1
- Roehrborn, C 874–5
- Roekevisch, E 106–7
- rofecoxib, cardiovascular
 risk 499
- Rogers, S 108–9
- Rollag, H 836–7
- Romeo, S 140–1
- Roos, A 186–7
- ropinirole, Parkinson's
 disease 374–5
- Rose, M 804–5
- Rosen, CL 788–9
- Rosen, G 710–11
- Rosenstock, J 142–3
- rosiglitazone, coronary
 artery disease in
 diabetes 81
- Rossouw, J 728–9
- Rostaing, L 826–7
- rotavirus vaccination 522–3

- Rothwell, P 354–5
 Rotondano, G 216–17
 Roujeau, J 120–1
 Rovers, MM 770–1, 772–3, 782–3, 786–7
 Rowan, A 282–3
 Rowe, J 296–7
 RTOG 9508 690–1
 Rudd, R 480–1
 Rudolph, T 254–5
 Runzi, M 628–9
 Russell, G 412–13
 Rutgeerts, P 234–5
 Ruutu, M 890–1
 Ryall, R 638–9
 Ryan, E 132–3
- S**
- Sabeti, S 918–19
 Sacco, RL 356–7
 Sackett, David 34, 36–41, 50
 safe surgery checklist, WHO 544–5
 Saji, T 528–9
 Salanti, G 520–1
 salbutamol
 asthma 455, 456
 chronic obstructive pulmonary disease 461, 462, 466
 virus-induced wheeze 530
 salmeterol
 asthma 454–5
 chronic obstructive pulmonary disease 460, 462–3
 Salmon, L 854–5
 salpingostomy, tubal ectopic pregnancy laparoscopy vs laparotomy 710–11
 vs methotrexate 712–13
 sample size 12
 SANAD study
 Arm A 362–3
 Arm B 364–5
 Sanchez, J 526–7
 sanitarians 13–14
 sanocrysin 18–19
 Sarin, S 222–3
 scarlet fever 12
 SCD HEFT 92–3
 Schafer, Edward Albert 180
 Schanz pins, coated vs uncoated 860–1
 Schillinger, M 918–19
 schizophrenia
 atypical vs typical antipsychotics 400–1
 relapse prevention 402–3
 treatment-resistant 404–5
 Schlaff, W 732–3
 Schmidt, B 514–15
 Schmitt, J 104–5, 366–7
 Scholefield, J 632–3
 Schram, ME 106–7
 Schumacher, H 502–3
 Schüpbach, WM 702–3
 scleroderma lung disease 504–5
 Scott, CB 690–1
 scurvy 4, 8
 SEQUAMAT 334–5, 336–7
 search engines 40–1
 Sebag-Montefiore, D 640–1
 sedation
 propofol 160–1
 weaning protocol 666–7
 Seelig, T 776–7
 seizures
 after head injury 678–9
 prevention 720–1
 see also epilepsy
 selective serotonin/norepinephrine reuptake inhibitors (SNRIs), depression 391
 selective serotonin reuptake inhibitors (SSRIs), depression 390–1
 relapse prevention 393
 panic disorder 408–9
 Seljelberg, F 370–1
 Sellick manoeuvre 547
 Semmelweis, Ignaz 14
 Semons, Sir Felix 674
 sensitivity 49
 sensualism 11
 sentinel node biopsy vs axillary dissection 570–1
 melanoma 800–1
 sepsis
 international guidelines for management 662–3
 prevention with ultraclean air theatres 866–7
 septic shock, management of catecholamines 652–3
 corticosteroids 668–9
 early goal-directed therapy 172–3
 international guidelines 662–3
 Serruys, PW 84–5
 Sestak, I 566–7, 584–5
 Sesti, G 142–3
 Sever, P 60–1
 Shah, S 660–1
 Shakur, H 164–5
 Shapiro, A 132–3
 SHARP 428–9
 Sharpe, D 808–9
 Shaw, GB, *The doctor's dilemma* 26
 Shepherd, F 482–3
 Shortt, A 760–1
 shoulder pain 506–7
 Shumway, Norman 816–17
 Shuster, S 108–9
 sickle-cell disease 294–5
 Silberstein, SD 366–7
 sildenafil, erectile dysfunction 876–7
 Silva, P 710–11
 Simonneau, G 474–5
 simvastatin
 chronic kidney disease 428–9
 coronary artery disease 58–9
 Singer, J 404–5
 single-blind trials 43
 sirolimus
 diabetes mellitus 132
 coronary artery disease in 83
 kidney transplantation 822, 823
 skin cancer 826–7
 Sjonell, G 368–9
 skin cancer
 facial basal cell carcinoma 802–3
 kidney transplantation 826–7
 melanoma see melanoma
 Sleeper, LA 82–3
 sleeping position and sudden infant death syndrome 520–1
 smallpox 6, 9
 SMART 318–19
 Smeets, N 802–3
 Smit, W 768–9
 Smith, C 608–9
 Smith, Richard 348
 Smits, J 818–19
 smoking 22, 448
 cessation
 treatments 470–1
 Snow, John 13–14
 Sokol, L 406–7
 SOLD 587
 Solera, J 340–1
 Soper, D 258–9
 Sors, H 474–5
 SoS (Stent or Surgery) 598–9
 SOS (Swedish Obese Subjects) 140–1
 SOS-TIA 355
 Souhami, R 480–1
 specificity 49

- Sperduto, PW 690–1
 Sperling, R 524–5
 sphincterectomy,
 endoscopic 626–7
 spinal injury 677
 spinal metastases, decompressive surgery for 688–9
 Spiro, S 480–1
 spironolactone, heart failure 88–9
 spondylolisthesis, instrumentation for 698–9
 spontaneous awakening trials (SATs) 666
 spontaneous breathing trials (SBTs) 666, 667
 spontaneous preterm labour (SPL) 722–3
 spontaneous supratentorial intracerebral haemorrhage (SSIH) 680–1
 SPORT 699, 700–1
 SPRINT 862–3
 Sprung, C 668–9
 Spuls, P 112–13
 squamous cell skin cancer 826–7
 St Clair, W 492–3
 ST elevation myocardial infarction (STEMI)
 pre-hospital thrombolysis vs primary percutaneous intervention 64–5
 thrombus aspiration 66–7
 Starling, Ernest 180
 START 452–3
 Starzl, Tom 816–17
 statins
 chronic kidney disease 428–9
 coronary artery disease 58–9
 statistical significance 48
 statistics
 developments 12–14, 19–20
 terms 46–9
 Steele, R 640–1
 Steen, Stig 833
 Stenning, S 620–1
 Steno-2 146
 stents
 carotid artery stenosis 906–9
 peripheral arterial disease 918–19
 see also bare-metal stents; drug-eluting stents
 Stephens, RJ 640–1
 stereotactic radiosurgery (SRS) for brain metastases 690–1
 steroids see corticosteroids
 STICH 96–7, 680–1
 STICH II 681
 Stiell, I 152–3
 stimulants, ADHD 414–15
 Stocken, D 630–1
 Stöffler, A 278–9
 Stone, Reverend William 10
 STOP 2 295
 STREAM 64–5
 streptomycin
 brucellosis 340–1
 tuberculosis 4, 22, 330
 tuberculous meningitis 332
 stress ulcer
 prophylaxis 664–5
 stress urinary incontinence 872–3
 Strickland, J 812–13
 STRIDE 326–7
 Strohm, B 516–17
 stroke
 antiplatelet drugs 356–7
 care in dedicated units 350–1
 hormone replacement therapy 729
 ischaemic 352–3
 prevention
 carotid artery stenosis 900–9
 in children with sickle-cell disease 294–5
 extracranial–intracranial bypass surgery 686–7
 warfarin 266–7
 urgent treatment 354–5
 Stroke rt-PA Stroke Study Group 352–3
 Stroup, TS 400–1
 Stuart-Harris, C 464–5
 Stupp, R 692–3
 Su, S 658–9
 subarachnoid haemorrhage (SAH) 682–3
 subthalamic nucleus (STN)
 stimulation in Parkinson's disease 702–3
 succinylcholine vs rocuronium–sugammadex 552–3
 sudden infant death syndrome (SIDS) 520–1
 Sue, Eugène 26
 Sufi, F 632–3
 sugammadex, neuromuscular block reversal by 552–3
 sulfasalazine, rheumatoid arthritis 494–5
 sulfonylurea, diabetes mellitus 134, 135
 Sulkowski, M 324–5
 Sullivan, F 384–5
 sumatriptan, migraine 368–9
 Summers, D 830–1
 superficial femoral artery (SFA) disease 918–19
 supportive psychotherapy (SP), panic disorder 406, 407
 surgery, comparison in 7
 surgical safety checklist, WHO 544–5
 surgical stripping (SS), varicose veins 920–1
 Surviving Sepsis Campaign 662–3
 Sutherland, Earl 180
 Svensson, A 104–5
 Swan, I 384–5
 Swedburg, K 90–1
 Sydenham, Thomas 486
 Sylvester, R 894–5
 SYNTAX 84–5, 600–1
 syphilis 242
 antibiotic treatment 244–5
 systematic reviews, role of 50–1
 Szczepanski, L 496–7
 Szechinski, J 496–7
 Szmukler, G 412–13
- T**
 tacrolimus
 atopic eczema 105
 diabetes mellitus 132
 transplantation 816–17
 kidney 820, 822–3, 826
 liver 834, 835
 tamoxifen, breast cancer 560
 early 582–5, 587
 prevention 564–5, 566, 567
 tamsulosin, benign prostatic hyperplasia 874
 Tangen, C 886–7
 TAPAS 67
 Targan, S 234–5
 TARGET 774–5
 Tarnow-Mordi, W 722–3
 Tashkin, D 504–5
 TASTE 66–7
 taxanes, breast cancer 578–9
 Taylor, D 160–1, 722–3
 Taylor, M 922–3
 Tedesco-Silva, H 822–3
 Tegnander, A 842–3
 telaprevir, hepatitis 238–9
 telmisartan, stroke 356
 Temkin, NR 678–9

- temozolomide, grade 4 astrocytoma 692–3
 TEMPO 442–3, 490–1
 temporal lobe epilepsy (TLE) 704–5
 tenecteplase, myocardial infarction 64
 tenofovir, HIV 322–3
 tension-free vaginal tape (TVT) 872–3
 Teo, K 78–9
 Teperman, L 834–5
 ter Braak, B 852–3
 terbutaline, chronic obstructive pulmonary disease 466
 TERMPROM 724–5
 testosterone replacement, male hypogonadism 196–7
 thalidomide 27
 myeloma 302–3
 Theriault, R 588–9
 Thevenot, T 228–9
 Thi Phuong, L 338–9
 thiotepa, bladder cancer 894
 Thomas, Hugh Owen 840
 Thomas, KS 122–3
 Thomas, R 274–5
 Thompson, AJ 344–5
 Thompson, I 886–7
 Thompson, J 800–1
 throat soreness in children 786–7
 thrombolysis
 ischaemic stroke 352–3
 pre-hospital 64–5
 thromboprophylaxis after pulmonary embolism 472–3
 thrombus aspiration 66–7
 Thwaites, G 332–3
 Tibbs, PA 688–9
 tibial fracture
 stabilization 862–3
 ticagrelor, non-ST elevation acute coronary syndrome 70–1
 ticlopidine
 carotid artery stenosis 908
 non-ST elevation acute coronary syndrome 73
 Tierney, C 322–3
 TIMACS 76–7
 Timaran, CH 906–7
 tinzaparin, pulmonary embolism 474–5
 tiotropium, chronic obstructive pulmonary disease 460–1
 tipranavir, HIV 320
 Tiruvoipati, R 656–7
 tissue plasminogen activator, ischaemic stroke 352–3
 TOBY 516–17
 tolvaptan, polycystic kidney disease 442–3
 Tomlinson, G 554–5
 Tondo, L 398–9
 topiramate
 epilepsy
 generalized and unclassifiable 364–5
 partial-onset 362–3
 migraine prophylaxis 366–7
 TORCH 462–3
 Tornetta, P 862–3
 Tosteson, TD 700–1
 TOTAL 67
 total hip replacement
 revision 850–1
 sepsis prevention 866–7
 total knee replacement, sepsis prevention 866–7
 total mesorectal excision (TME), rectal cancer 638–9
 neoadjuvant radiotherapy 640–1
 Trainer, P 200–1
 tranexamic acid following trauma 164–5, 542–3
 transcatheter aortic valve implantation (TAVI) 608–9
 transfusion
 critical care 650
 platelet transfusion threshold 292–3
 see also red cell transfusion
 transient ischaemic attack 354–5
 transplantation 815–37
 transurethral resection of bladder tumour (TURBT) 894–5
 trastuzumab, breast cancer 563, 586–7
 trauma 839–67
 head see head injury
 tranexamic acid following 164–5, 542–3
 TREAT 426–7
 triamcinolone
 diabetic retinopathy 756–7
 otitis externa 768–9
 TRICC 290–1
 tricyclic antidepressants (TCAs)
 depression 390–1
 relapse prevention 393
 peripheral neuropathy 383
 trifluridine, ocular herpes simplex 763
 trilabium 870
 trimethoprim–sulfamethoxazole resistance 338
 Trinquart, L 908–9
 triple-blind trials 43
 TRITON 71
 tropical medicine 329–45
 Trousseau, Armand 17
 tubal ectopic pregnancy
 see ectopic pregnancy, surgery
 tuberculosis (TB) 448
 antibiotic therapy 330
 HIV-associated 326–7
 sanocrysin 18–19
 streptomycin 4, 22
 tuberculous meningitis (TBM) 330, 332–3
 tubular compression
 bandages, ankle sprain management 166–7
 TUMORAPA Study Group 826–7
 tumour necrosis factor- α (TNF- α) antagonists
 ankylosing spondylitis 500–1
 rheumatoid arthritis 488–95
 Turrisi, A 478–9
 type 1 diabetes mellitus (T1DM)
 insulin pump therapy vs multiple daily insulin injections 130–1
 islet cell transplantation 132–3
 type 1 errors 43
 type 2 diabetes mellitus (T2DM) 128
 bariatric surgery and cardiovascular risk 140–1
 calorie restriction, benefits of 144–5
 chronic kidney disease 426–7
 coronary artery disease revascularization vs medical care 80–1
 GLP-1 analogues 142–3
 intensive blood pressure control 138–9
 intensive glucose control 134–5
 intensive glucose lowering 136–7
 multiple risk factor intervention 146–7

type 2 errors 43
 typhoid 18–20
 antibiotic therapy 338–9
 inoculation 19–20

U

UKPDS 134–5
 UKSAT 912–13
 ulcerative colitis (UC) 232–3
 Ulmsten, U 872–3
 ultraclean air theatres 866–7
 ultrasound (US)
 abdominal aortic aneurysm screening 910–11
 developmental dysplasia of the hip 842–3
 haematuria assessment in bladder cancer 892–3
 unenhanced spiral computed tomography, renal colic 878–9
 unfractionated heparin (UFH)
 miscarriage, recurrent 714–15
 non-ST elevation ACS 69, 72–3
 pulmonary embolism 472–3
 comparison with LMWH 474–5
 unicompartmental knee replacement (UKR), cemented vs cementless 858–9
 upper gastrointestinal bleeding
 with cirrhosis 224–5
 intravenous proton pump inhibitor 220–1
 red cell transfusion 218–19
 upper respiratory tract infections (URTIs) in children, recurrent 782–3
 ureteral catheterization 882–3
 ureterorenoscopy (URS) 884–5
 urinary incontinence, stress 872–3
 urology 879–95
 ustekinumab, psoriasis 116–17
 uterine fibroids 734–5

V

VA/NIH Acute Renal Failure Trial Network 422–3
 vacuum-assisted closure (VAC) 806–7
 vaginal birth for breech presentation 726–7
 Vaidyanathan, S 784–5
 valaciclovir (VACV)
 Bell's palsy 385
 genital herpes prophylaxis 256–7
 treatment 254–5
 Valazques, EJ 96–7
 valdecoxib, cardiovascular risk 499
 valganciclovir, cytomegalovirus infection 836–7
 congenital 527
 valproate
 generalized and unclassified epilepsy 364–5
 new-onset epilepsy 282
 partial-onset epilepsy 362
 valve replacement, mechanical vs biological 606–7
 Van Assche, G 232–3
 van Balen, F 768–9
 Van den Aardweg, MTA 782–3
 van den Bent, MJ 692–3
 van den Bernd, G 806–7
 van der Heijde, D 490–1
 van der Lely, A 200–1
 van der Meijden, A 894–5
 Van der Post, JA 716–17
 van der Windt, D 506–7
 van Domburg, R 186–7
 van Erkell, A 852–3
 Van Helmont, JB 7
 van Kobyletzki, L 104–5
 van Noord, J 460–1
 Vandemheen, K 152–3
 Vanner, R 546–7
 Vanrenterghem, Y 820–1
 variceal bleeding 222–3
 varicose veins (VVs) 898
 surgical technique 920–1
 vascular endothelial growth factor antagonists, age-related macular degeneration 748–9
 vascular surgery 897–23
 vasopressin, septic shock 652–3
 VASST 652–3
 vemurafenib, metastatic melanoma 124–5
 Venel, Jean André 840
 venereal disease (VD) 242
 venlafaxine, depression 391
 venous
 thromboembolism (VTE) in cancer 308–9
 oral anticoagulation 310–11
 prophylaxis 472–3
 venous ulcers 922–3
 ventilation
 high-frequency oscillation (HFO) for acute respiratory distress syndrome 660–1
 obstructive sleep apnoea 790–1
 weaning protocol 666–7
 see also continuous positive airways pressure; non-invasive positive pressure ventilation; non-invasive ventilation
 ventricular fibrillation (VF)
 cardiac arrest, hypothermia after 170–1, 670–1
 ventricular tachycardia (VT)
 cardiac arrest, hypothermia after 170–1
 Vermesh, M 710–11
 Veronesi, U 570–1, 798–9
 Vesikari, T 522–3
 vestibular rehabilitation (VR) for chronic dizziness 778–9
 Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group 594–5
 Viale, G 570–1
 Vicini, C 790–1
 vicroviroc, HIV 320
 VICTOR 836–7
 Vignetti, M 304–5
 VIGOR 499
 Villanueva, C 218–19
 vinblastine, non-small cell lung cancer 480
 Vincenti, F 820–1
 Vincken, P 852–3
 Vincken, W 460–1
 vindesine, non-small cell lung cancer 480
 vinorelbine, non-small cell lung cancer 480
 viral warts 102
 vitamin D, and falls 270–1
 vitamin E, and mild cognitive impairment 274–5

vitiligo 102
 Vlug, M 646–7
 Volodos, Juan C. 898
 vomiting,
 post-operative 556–7
 von Brevern, M 776–7

W

Wallace, A 730–1
 Wallentin, L 70–1
 Walsh, Patrick 870
 warfarin
 atrial fibrillation 266–7
 valve replacement 606
 warts
 genital 252–3
 viral 102
 Webster, J 202–3
 Wedel, H 60–1
 Weeden, S 622–3
 Wegener's
 granulomatosis 444
 Weigelt, J 848–9
 Weinstein, JN 700–1
 Weiser, T 544–5
 Weisman, M 488–9
 Wells, G 152–3, 290–1
 Wells, P 176–7
 Werutsky, G 576–7
 Wheatley, D 606–7
 Wheelahan, T 804–5
 wheeze,
 virus-induced 530–1
 WHI 728–9
 whiplash injury
 management 168–9
 White, P 416–17
 whole-brain radiotherapy
 (WBRT) 690–1
 Whyte, W 866–7
 Wickerham, D 564–5
 Wickman, M 572–3
 Wiebe, S 704–5
 Wilensky, AJ 678–9
 Willett, W 270–1
 Williams, H 110–11
 Williams, M 168–9, 608–9
 Williamson, J 284–5
 Williamson, P 784–5
 willow bark (*Salix alba*) 10
 Wilson-MacDonald, J 696–7
 Wind, J 646–7
 Wisconsin Cystic Fibrosis
 Neonatal Screening
 Study Group 518–19
 WISDOM 729
 Withering, William 6, 10, 56
 Wo, JM 792–3
 Wong, B 210–11
 Wong, W 210–11
 Woodhams, S 878–9
 Woodle, ES 824–5
 World Health Organization
 (WHO) safe surgery
 checklist 544–5
 Wormser, G 342–3
 wound therapy, vacuum-
 assisted closure vs gauze
 therapy 806–7

Wright, R 272–3
 Wu, J 220–1
 Wyre, S 810–11

X

xenon laser photoco-
 agulation, diabetic
 retinopathy 752–3

Y

Yardley, L 778–9
 Yates, David 150
 Yeung, J 832–3
 Young, D 660–1
 Young, J 780–1
 Yu, LM 684–5
 Yusuf, S 68–9, 356–7

Z

Zannad, F 88–9
 zidovudine, maternal–
 infant transmission of
 HIV 524–5
 ziprasidone,
 schizophrenia 400
 zoledronic acid, Paget's
 disease 194–5
 zonisamide, generalized
 and unclassifiable
 epilepsy 365
 Zuithoff, N 768–9
 Zwart, S 786–7

